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CONGENITAL HYPOPROTHROMBINEMIC STATES
ARMAND J. QUICK, M.D., ET AL.

CLINICAL SYNDROMES ASSOCIATED WITH HYPERNATREMIA
HAROLD M. SCHOOLMAN, M.D., ET AL.

ACETAZOLEAMIDE (DIAMOX) DIURESIS
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ADULT AGAMMAGLOBULINEMIA
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JANUARY 1955
VOLUME 95 NUMBER 1

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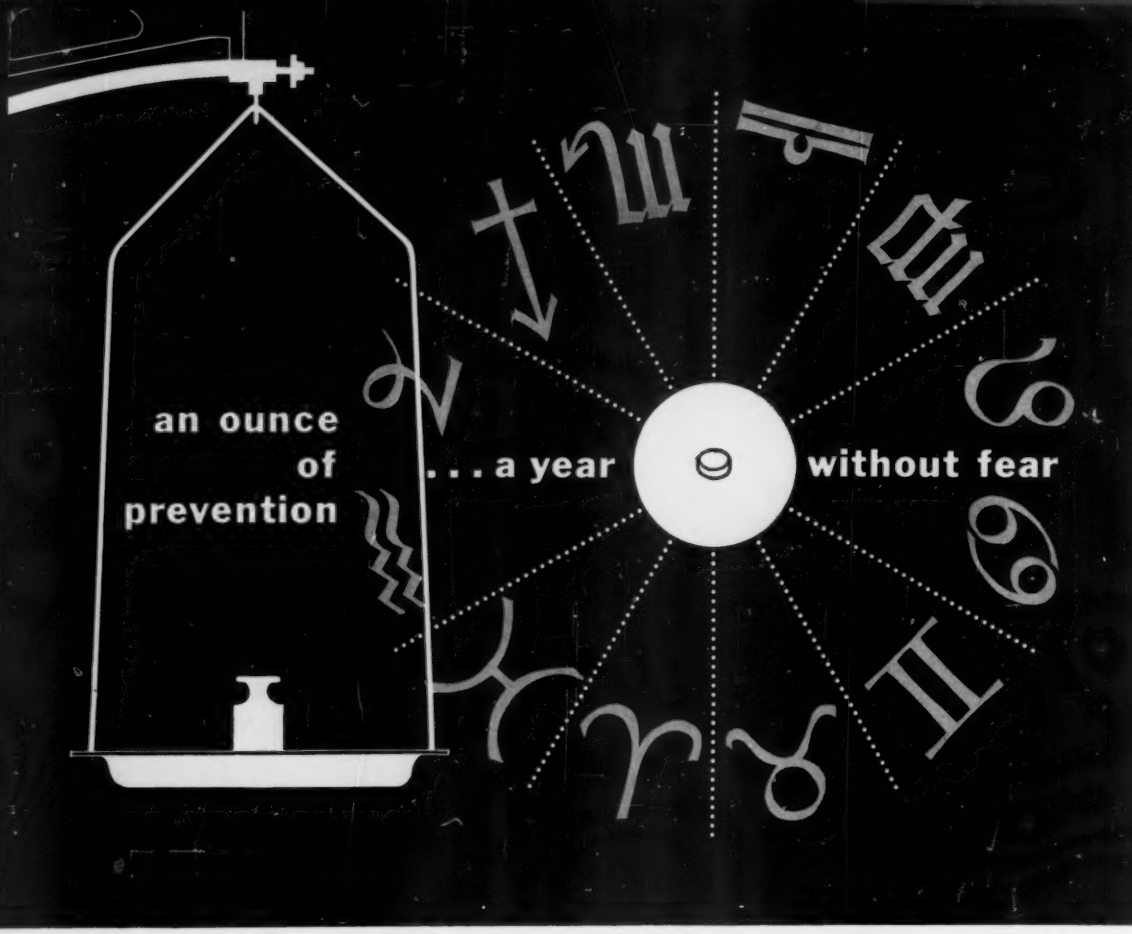

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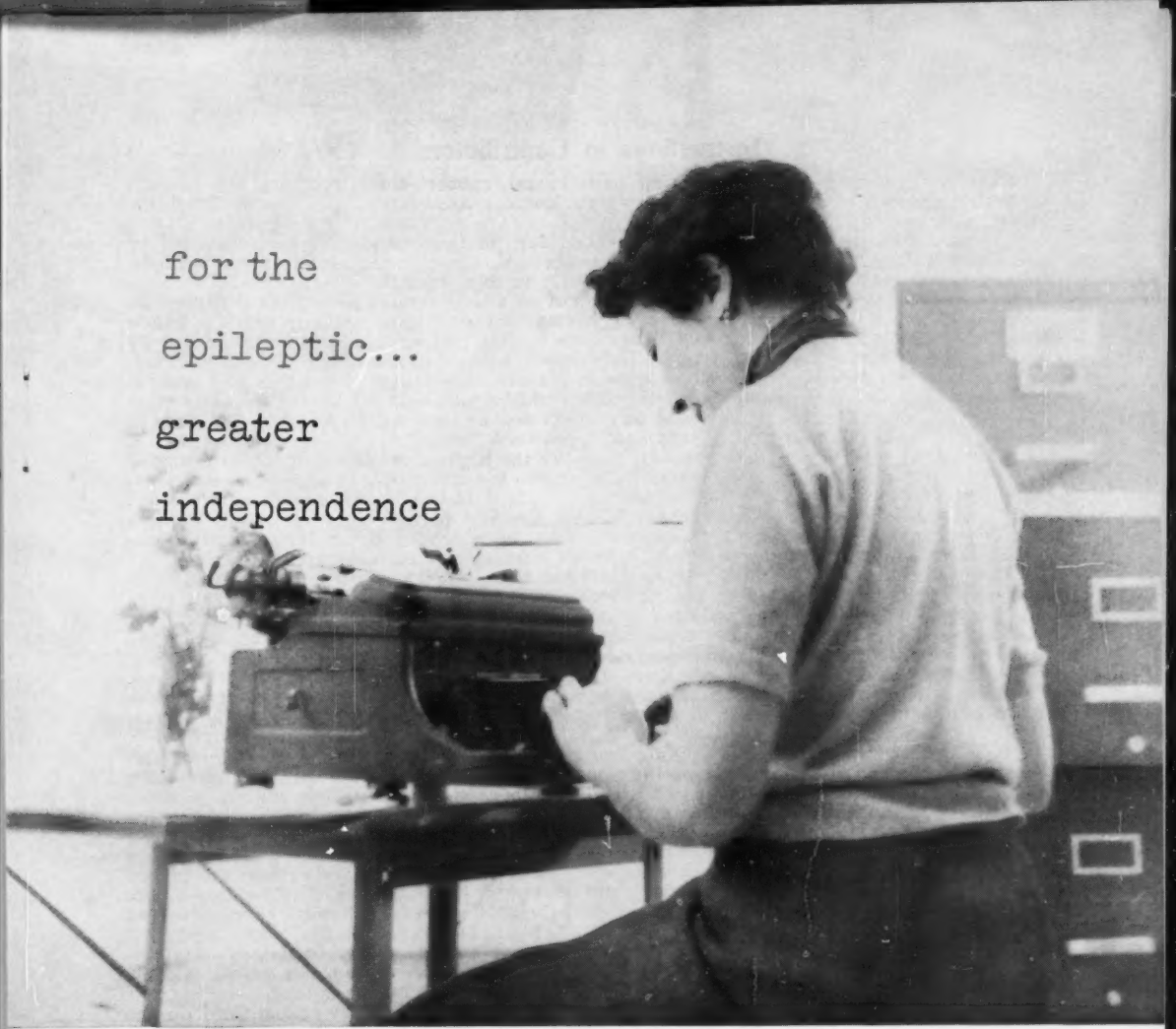

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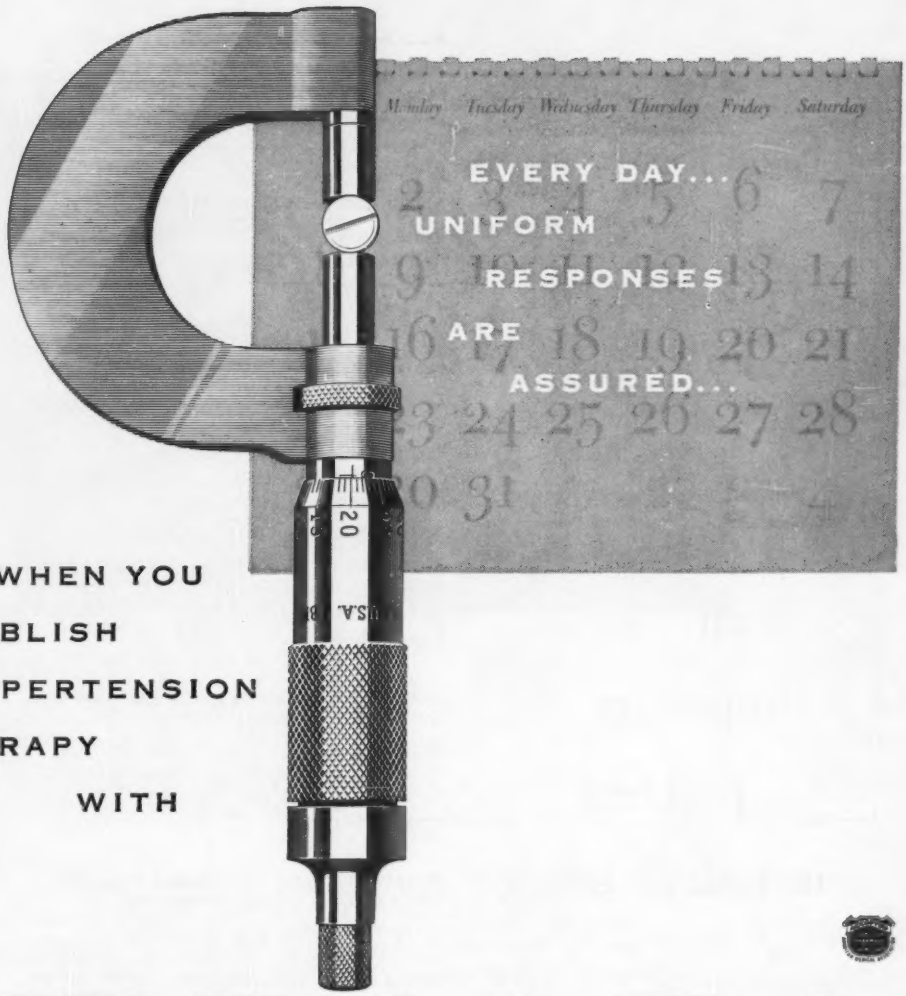

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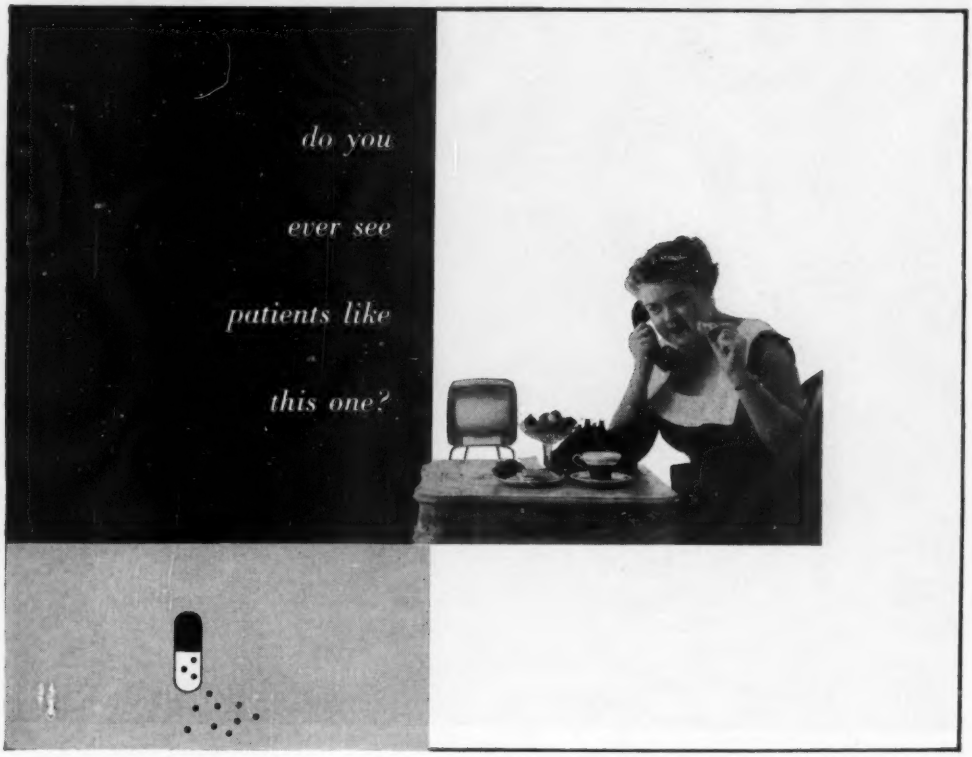

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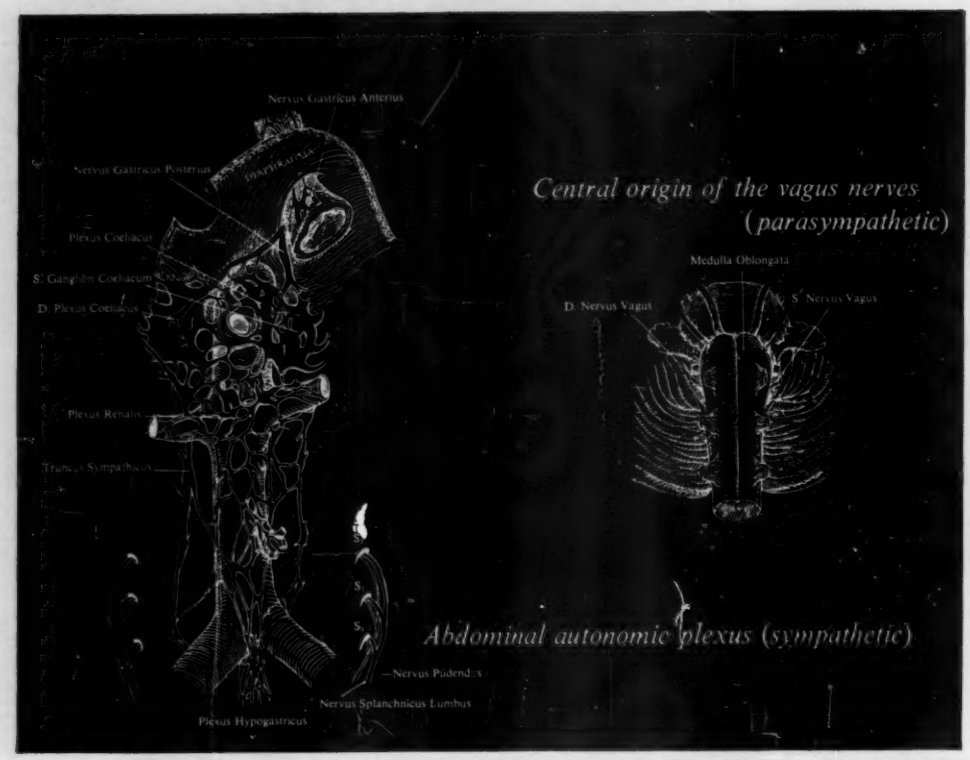

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1. Zupko, A. G.: Pharmacology and the General Practitioner, GP 7:55 (March) 1953.

2. McHardy, G. G., and Others: Clinical Evaluation of Methantheline (Banthine) Bromide in Gastroenterology, J.A.M.A. *147*:1620 (Dec. 22) 1951.

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LETTER FROM THE EDITORS

WE HOPE that you will like the "new look" of the ARCHIVES. The cover has been completely redesigned, and illustrations and space have been rearranged to present a maximum amount of material in the minimum compass compatible with good readability. If you disapprove, the editors accept a full share of responsibility for these changes, because they were consulted freely during the planning. The editors were somewhat disturbed by the fact that this is the second change in the format of the ARCHIVES since its publication began, in 1908. However, they were glad to accede to the new proposals for the cover provided it contained at least a partial list of the table of contents, a suggestion which was readily accepted by the business management.

It has been felt, in line with the policy of the Editorial Board to attempt to keep abreast of the major interests of all internists by such innovations as the series of papers on "Treatment," the Scientific Exhibits, editorials on timely topics, etc., that some change in the physical form of the ARCHIVES was in order. The Board feels that the changes made at the A. M. A. offices are well conceived and executed. The editors will strive to continue to do their part in selecting new, reliable, and informative material for the readers and in presenting it without undue delay.

CHIEF EDITOR

CONGENITAL HYPOPROTHROMBINEMIC STATES

ARMAND J. QUICK, M.D.; ANTHONY V. PISCIOTTA, M.D., and CLARA V. HUSSEY, M.S., Milwaukee

THE DISCOVERY of a case of congenital hypoprothrombinemia in 1941 by Rhoads and Fitz-Hugh [1] marked the beginning of an important advance in the study of hemorrhagic diseases. This case had been diagnosed and regarded as hemophilia for nine years. Only after the prothrombin-time test became available was it possible to differentiate such a condition readily from hemophilia. From the early studies * it became evident that cases of this type were congenital and likely familial. All were tacitly accepted as true hypoprothrombinemia. The discovery of the labile factor (proaccelerin, Factor V, or ac-globulin) in 1943 clearly demonstrated that the prothrombin time could be prolonged by a deficiency of this new factor, and the prediction that such a lack might cause a hemorrhagic disease [9] was borne out when, less than two years later, Owren [10] reported a patient with a bleeding tendency who lacked this agent. Shortly thereafter, members of two families were studied who had a prolonged prothrombin time.† Significantly, the blood from an affected member of one family corrected the blood of the second family. Since the labile factor was normal in both, it became necessary to conclude that another factor in addition to prothrombin and labile factor had to be considered. More recently, the studies of Alexander and co-workers,‡ Jacox,[15] Koller and co-workers,[16] Owren,[17] Mann,[18] and others clearly established the existence of at least one more accessory factor, which for convenience and simplicity may be designated as stable factor.

Obviously, the term hypoprothrombinemia as commonly accepted includes several distinct clinical entities. Since the majority of congenital hemorrhagic conditions are apt to lack only one clotting factor, such cases offer a naturally created physiological experiment, which can furnish much valuable information. The opportunity to study various types of congenital hypoprothrombinemic states repeatedly over a period ranging from one to nine years has furnished data on their clinical course, diagnosis, treatment, and hereditary pattern and also on the nature of the various prothrombin factors.

METHODS

Blood was always collected with a silicone-coated syringe and needle and transferred to test tubes similarly coated and immersed in an ice bath. The various clotting tests were done in uncoated glass test tubes (13 by 100 mm.) at 37 C.

Prothrombin Time.—The test was carried out as originally described,[19] using as the thromboplastin reagent acetone-dehydrated rabbit brain. With this reagent and 0.01 M calcium chloride, a prothrombin time of 12 seconds is consistently obtained on fresh normal human plasma.

Total Prothrombin Time.—The principle of this test is to measure the prothrombin after all of the prothrombinogen is converted to free prothrombin. The conversion of prothrombinogen may be effected by either storing oxalated plasma at 4 C. in a glass container for 24 to 48 hours or by removing the platelets with high-speed centrifugation and coagulating the platelet-poor plasma in a glass test tube at 37 C. Owing to the absence of platelets, only traces of thromboplastin can form, and therefore only a negligible amount of prothrombin is consumed.

From the Department of Biochemistry, Marquette University School of Medicine.

This work was supported by a grant (H-1612 C7) from the National Heart Institute, National Institutes of Health, United States Public Health Service.

Drs. Mila Pierce and Albert T. Kwedar gave us opportunity to study their patients and permission to include our findings in this paper, and Dr. Benjamin Alexander studied the plasma of one of the patients.

* References 2-8.

† References 11 and 12.

‡ References 13 and 14.

Procedure 1: Two cubic centimeters of oxalated plasma is placed in an open test tube kept in a refrigerator for 24 to 48 hours. To 0.1 cc. of the stored plasma, 0.01 cc of deprothrombinized rabbit plasma is added, and the prothrombin time of the mixture is determined. The rabbit plasma resupplies labile factor, which disappears during storage.

Procedure 2: To 4.5 cc. of freshly drawn blood, 0.5 cc. of 0.2 M sodium citrate is added in a silicone-coated test tube. After being centrifuged for 10 minutes at 4,000 rpm, the plasma is carefully removed and transferred to a silicone-coated heavy-wall test tube and centrifuged for 30 minutes at 10,000 rpm. One cubic centimeter of this plasma is removed and mixed with 0.1 cc. of 0.3 M calcium chloride in a glass test tube and incubated at 37 C. The fibrin is removed as it is formed by wrapping it about a glass stirring rod, and 15 minutes after coagulation is complete the prothrombin of the serum is determined. One-tenth cubic centimeter of the serum is blown into a mixture of 0.1 cc. of deprothrombinized rabbit plasma, 0.1 cc. thromboplastin reagent, and 0.1 cc. 0.02 M calcium choride, and the clotting time is accurately measured. The results of both procedures agree very closely.[20] The range for normal plasma is eight to nine seconds.

Prothrombin Consumption Time.—Two cubic centimeters of blood is placed in each of two test tubes which are in a water bath at 37 C. Fifteen minutes after clotting is complete the first tube is centrifuged and again placed in the water bath. After 30 minutes the second tube is centrifuged, and 30 minutes later the prothrombin in the serum of both tubes is determined exactly as outlined in the previous test.

Labile-Factor Estimation.—When oxalated human plasma is stored at 4 C., the prothrombin time increases, owing to a progressive loss of labile factor. Stored plasma becomes a satisfactory medium for testing the concentration of labile factor in fresh plasma. For this purpose stored plasma having a prothrombin time of about 40 seconds is used. To test the labile-factor concentration, 0.01 cc. of plasma to be tested is mixed with 0.09 cc. of stored plasma and the prothrombin time of the mixture determined. If the labile factor is normal, the mixture has a prothrombin time of 16 to 19 seconds.

Stable Factor Preparation.—The method of Duckert, Koller, and Matter[21] for obtaining and purifying Factor VII from oxalated human serum was used exactly as described. Aged human serum was found equally satisfactory.

Deprothrombinized Rabbit Plasma.—The method for the adsorption of prothrombin with tricalcium phosphate from rabbit plasma was carried out as previously described.[20] Such plasma is rich in labile factor but lacks prothrombin and stable factor.

REPORT OF CASES

Congenital hypoprothrombinemia, Type I (panhypoprothrombinemia)

FAMILY 1.—In this family, two brothers have had a bleeding condition since early infancy. Their parents, three brothers, and one sister are normal. One brother, who died in infancy following an operation for intestinal obstruction, never showed any signs of a bleeding tendency and was presumably normal. When this family was reported in 1947,[12] the concept of prothrombinogen had not been developed and the existence of stable factor was unknown.

T. B. was born in 1941. He bled for over two months following circumcision done during the first week. Although he bruised easily, he had no further bleeding until he was 5½ years old, when he hemorrhaged profusely following the extraction of a tooth, which required a transfusion. He has bled from cuts in his mouth and on his tongue. Bleeding from cracked lips during winter has been troublesome to control. An attack of hematuria was stopped by a transfusion. During the past two years he has had pain and swelling of his right ankle. It is probable that it was a hemarthrosis, but it caused no permanent impairment of his joint. Except for these few serious bleeding episodes, his bleeding disease has run a mild course and has not restricted his activities.

B. B., who is a brother of T. B., was born in 1945. He has bruised easily since infancy, and during his first year he had intestinal bleeding. At the age of 2 years he had a large hematoma on his forehead, following a blow. He required a transfusion to control the bleeding from biting his tongue. At age 3 years he had hematuria, which was promptly stopped by transfusing 250 cc. of fresh blood. On two occasions he has bled into his left popliteal space. During the past year he had a massive hemorrhage into his left calf muscle, which responded favorably to 50 mg. vitamin K_1 emulsion given intravenously. He has more bleeding episodes than his brother, which is best explained by his greater activity and lesser caution to avoid injury.

Clinically, the condition of these two boys resembles mild hemophilia, but the prolonged prothrombin time furnishes the key to the diagnosis. As will be discussed later, the blood of these two subjects has a normal concentration of both labile and stable factors; therefore, one is justified to conclude that the prolonged prothrombin time is due to a true lack of prothrombin. Curiously, the prothrombin time of the blood of both boys was 19 to 20 seconds for several years but during the past three years has varied between 21 and 26 seconds. After injection of vitamin K_1 the prothrombin time was temporarily reduced to 19 seconds in B. B. The total prothrombin time is also prolonged, ranging from

16 to 21 seconds, which indicates that both the free and the total prothrombin are reduced. Table 1 contains a summary of the laboratory findings.

Since the coagulation defect as determined by various tests is quantitatively the same in both boys and since it was present at birth, it is certain that the disease is congenital and familial. Whether it is hereditary cannot be answered. The prothrombin time is normal in all the other members of the family, including the maternal and paternal grandparents (Fig. 1). If the condition is hereditary, the defective gene must be recessive.

FAMILY 2.—The youngest of four sisters is a bleeder; the others are normal. The father is well, never has had any abnormal bleeding, and has a prothrombin time of 12 seconds. The mother died of heart disease when the patient was one month old.

V. A. was born Oct. 23, 1950. At the age of five months, following the removal of a lipoma from the abdominal wall, she bled profusely and required a transfusion. Prior to the operation she had no bleeding nor was bruising observed. After she began to walk, she had frequent deep hemorrhages into her muscles, which required transfusions. When she was one year old, her condition was diagnosed as hypoprothrombinemia at Barnes Hospital at St. Louis. It was found that vitamin K did not correct the prothrombin time. She bruises easily and has bled from a cut in her gum. For the past year she has developed periodically a characteristic lesion in her left thigh. It begins as a red ring which enlarges and becomes black and blue and very hard. She is then unable to walk. After a transfusion of plasma, the swelling and pain disappear in about three days. After three weeks, a new hemorrhage occurs. She has had no epistaxis, hematuria, or hemarthrosis.

A prothrombin time of 36½ seconds was found on Nov. 9, 1953, when she was first studied. On June 25, 1954, her prothrombin time was 35 seconds and all the other findings were essentially the same as in the first study. These are summarized in Table 1.

The bleeding condition of this girl is more severe than that of the two boys of Family 1, but the basic defect is the same, namely, a deficiency of both free and total prothrombin. This accounts for the similarity of findings in the three patients. In each, the clotting time is slightly prolonged, the prothrombin time and total prothrombin time are in the hemorrhagic range, and the prothrombin consumption time is very prolonged. When the plasma of V. A. was mixed in varying proportions with that of T. B., no mutual correction occurred (Fig. 2).

TABLE 1.—*Characteristic Laboratory Findings in Hypoprothrombinemia of Types I and II and Stable-Factor and Labile-Factor Deficiencies* *

		Congenital Hypoprothrombinemia			Stable-Factor Deficiency		
		Type I		Type II,			Labile-Factor
	Normal	B. B.†	V. A.	R. F.	M. P.	H. S.	Deficiency
Coagulation time (Lee-White), min.	5-8	12-16	14-17	5-8	5-7	7-9	..
Prothrombin time, sec.							
Plasma	12	19-26	37	16	35-70	27-41	40
Plasma + normal plasma (1:1)	12	12	12½	14	12	12	12
Plasma + stored plasma (1:1)	12	12	12	14	12	12	40
Plasma + fresh $Ca_3(PO_4)_2$ plasma (1:1)	12	32	38	14-18	45	33	12
Plasma + stable factor	12	19-26	37	13	12	12	40
Total prothrombin time, sec.	8-9	16-21	25	8-9	25	18	8-9
(After addition of stable factor), sec.	8-9	16-21	25	8-9	10	8	8-9
Prothrombin consumption time, sec.	16-35	180	165	36	65	73	8-9
(After addition of stable factor), sec.	16-35	180	165	36	27	31	8-9
Labile-factor activity, sec.	16-19	17	17	16	16	16	40

* The tourniquet test, bleeding time, clot retraction, platelet count, and fibrinogen concentration in all cases have been normal, except that in the case of M. P. a bleeding time of five minutes was obtained on one occasion.
† The findings of T. B. of Family 1 were almost identical with those of his brother B. B.

Congenital hypoprothrombinemia, Type II (hereditary hypoprothrombinemia)

FAMILY 3.—In May, 1943, a medical student, R. F., was found to have a prothrombin time of 16 seconds. This value has remained constant and is not influenced by large doses of vitamin K. The subject is in excellent health and has had no abnormal bleeding. His sister, M. F., had severe menorrhagia at the time of puberty, but it is uncertain whether the coagulation defect played a role. Her prothrombin time as well as that of the mother is 16 seconds. The mother had five deliveries without any hemorrhage and at no time had abnormal bleeding. It is obvious that the clotting defect is subclinical.

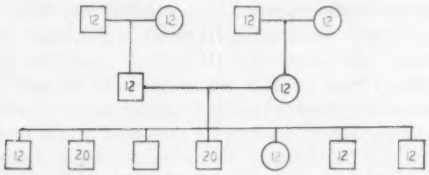
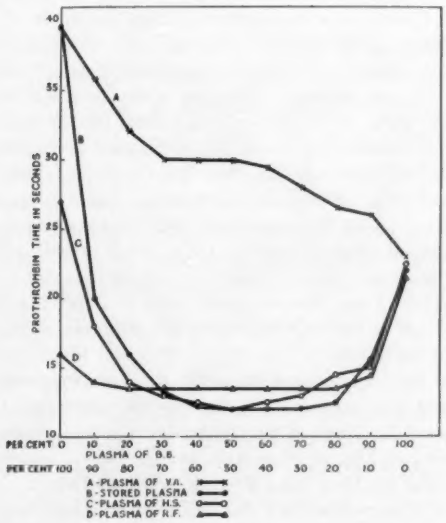


Fig. 1 (Family 1).—Pedigree of hypoprothrombinemia Type I. The third son died in early infancy. He showed no signs of a bleeding tendency. The number within the circle or square is the prothrombin time in seconds.

The hereditary pattern of this family is interesting (Fig. 3). The mother, one son, and the daughter have a prothrombin time of 16 seconds, while the father and the other three sons have a normal value, of 12 seconds. Obviously, the defect is transmitted quantitatively.

The hypoprothrombinemia of Type II is readily distinguished from that of Type I. The simplest test is to mix the patient's plasma with an equal volume of fresh normal plasma. If the person has Type II hypoprothrombinemia the mixture will have a prothrombin time greater than 12 seconds. Thus, the mixture of R. F. plasma with normal always has a prothrombin time of 13½ to 14 seconds. When the plasma of R. F. is mixed with the plasma of T. B., who has panhypoprothrombinemia, a mutual but incomplete correction occurs, and, at the ratio of 1 : 1, the prothrombin time is 13½ seconds (Fig. 2). It is clear, therefore, that Types I and II are distinct entities. Both lack free prothrombin, but Type I also lacks prothrombinogen, whereas Type II does not.

Fig. 2.—The effect on the prothrombin time when plasma from a patient with congenital hypoprothrombinemia of Type I (panhypoprothrombinemia) is mixed with plasmas of Types I and II hypoprothrombinemias or stable- and labile-factor deficiencies. It will be noted that no mutual correction occurred when the plasmas of B. B. and V. A. were mixed, since both belong to Type I hypoprothrombinemia. Mixed Types I and II (R. F.) did not produce complete correction. When B. B.'s plasma was mixed with plasma lacking either the stable factor (H. S.) or labile factor (stored plasma), a complete correction was obtained when the ratio of the two plasmas was 1 : 1.



Stable-factor deficiency

FAMILY 4.—In this family the daughter, aged 3, has been a severe bleeder since birth. One son and both parents have never bled abnormally. No history of bleeding is known in either the father's or the mother's family.

M. P. was born in April, 1951. At 3 weeks she passed blood in her stools, and at 3 months she had a blood blister on her tongue which bled sufficiently to produce tarry stools. When she was 10 months old she had a hematoma in her left upper arm, and two months later she had a massive hemorrhage in the calf of her left leg. She had a blood blister with eruption of every tooth, but only one bled sufficiently to require a transfusion. At the age of 18 months she had an intracranial hemorrhage, which caused convulsions and a temporary paralysis of the right arm and leg. She made a rapid and complete recovery. She continues to have numerous hemorrhages, especially into her muscles and subcutaneous tissues, and requires frequent transfusions. She has had no epistaxis except a blood-stained purulent discharge during a severe upper respiratory infection. She has had no hematuria.

She was first studied March 19, 1953. Previous to this, she had been diagnosed as having congenital hypoprothrombinemia, at Billings Hospital, Chicago. Our studies were repeated in July and August and

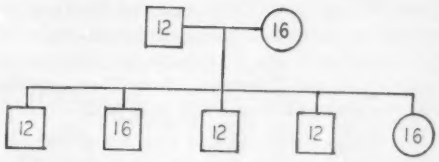
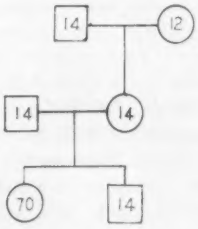


Fig. 3 (Family 3).—Pedigree of hypoprothrombinemia Type II.

Fig. 4 (Family 4).—Pedigree of stable-factor deficiency.



again a year later. The essential findings are summarized in Table 1. The prothrombin time at the first examination was 35 seconds, but subsequently it was 65, 72, and 70 seconds. The total prothrombin time has remained consistently at 24 to 25 seconds.

It is highly significant that both her parents, her brother, and her maternal grandfather have a slightly prolonged prothrombin time but that her maternal grandmother is normal (Fig. 4). When her plasma is mixed with that of the grandmother, correction occurs, i. e., the prothrombin time becomes 12 seconds, but the plasmas of her parents, her brother, and her maternal grandfather cause appreciably less correction (Table 2). Interestingly, the prothrombin time of her parents varies. Values ranging from

TABLE 2.—*Effect of Mixing Plasma of M. P. with That of Her Grandmother, Who Is Normal, and of Her Mother and Grandfather, Who Have the Abnormal Trait*

Plasma of M. P., Cc.	Test Plasma, Cc.	Prothrombin Time, Sec.		
		Grandmother's Plasma	Mother's Plasma	Grandfather's Plasma
0.1	....	65	65	70
0.09	0.01	18	25	27
0.08	0.02	14	20	21
0.07	0.03	13½	19	18
0.06	0.04	13	19	17
0.05	0.05	12	17	16
0.04	0.06	12	16	16
0.03	0.07	12	16	15½
0.02	0.08	12	15	15
0.01	0.09	12	15	14½
....	0.1	12	14	14

13½ to 16 seconds have been found, and similar observations have been made on the affected members of Family 5.

The patient's prothrombin time can be corrected by the addition of small amounts of serum, which correction differentiates her disease from true hypoprothrombinemia. Her total prothrombin is low when measured by the unmodified procedure, but when aged serum is added a value that is the same as that of normal blood is found (Table 1).

FAMILY 5.—This family consists of the patient, her daughter, and two grandchildren.

H. S. is a 53-year-old widow. She had no history of bleeding in childhood, and she did not bruise easily. She had profuse menstruation during puberty. She had two children with no abnormal bleeding following delivery. Two years after the birth of her second child, she had a gynecological operation to control menorrhagia. She bled postoperatively and required a transfusion of blood. Severe uterine bleeding recurred. Nearly 20 years ago she bled sufficiently from an extraction of a tooth to require a transfusion. The removal of a vaginal cyst also caused bleeding which was controlled only after a transfusion. She has had no recent hemorrhages but bruises moderately. For the past 20 years, she has suffered from pretibial pain of her right leg and has frequently taken a medicine containing cinchophen to obtain relief. A markedly prolonged prothrombin time was accidentally discovered during a routine blood study at the Milwaukee County Hospital.

The pertinent laboratory findings are summarized in Table 1. The patient's prothrombin time is generally about 26 to 27 seconds, but it has been 45 seconds. The total prothrombin time (uncorrected for stable factor) is usually about 18 seconds. Compared with M. P., this patient has a definitely shorter prothrombin time and, clinically, she is a much milder bleeder. The prothrombin time of this patient, like that of M. P., is corrected by aged serum and by partly purified stable factor. When her plasma is mixed with increasing amounts of plasma from B. B. of Family 1, who has panhypoprothrombinemia, a mutual correction of the two plasmas occurs, and, at a ratio of 1:1, the prothrombin time is 12 seconds (Fig. 2). This clearly suggests that one has normal prothrombin and the other has an excess concentration of stable factor. Dr. Benjamin Alexander, who studied a sample of her plasma, found a normal prothrombin level by the two-stage method and a stable-factor (serum prothrombin conversion accelerator; S.P.C.A.) concentration of 14%, using Owren's technique.

From the history it was uncertain whether in this case the deficiency of stable factor was congenital or was caused perhaps by cinchophen, but the finding that her daughter has a prothrombin time of 14 seconds instead of the normal, of 12 seconds, makes it fairly certain that the patient is homozygous in regard to the defective gene and that her children must therefore be heterozygous.

FAMILY 6.—The mother of this family is the sister of the patient J. L., the case of hypoprothrombinemia reported by Hagen and Watson [22] and Frick and Hagen.[23] According to the latter authors, the defect in this patient is a familial lack of stable prothrombin conversion factor. In their first publication, they reported that their patient's mother and three siblings had prothrombin times ranging from 16 to 18 seconds but that the father had a normal value. In view of the evidence presented in this paper that a bleeder is homozygous, having received the defective gene from both parents, it would be desirable to recheck the prothrombin time of the father.

Mrs. C. has a prothrombin time of 14 seconds, and her husband has the normal value, of 12 seconds. Three of the children have a prothrombin time of 13½ to 14 seconds, and one has 12 seconds (Fig. 5). None has a bleeding tendency. This family illustrates how high the incidence of transmission

of a defective gene may be and how hazardous it is for even distant relatives of an affected family to intermarry.

LABILE-FACTOR DEFICIENCY

From the reported cases, it is fairly well established that the condition is familial and hereditary. While the authors have had no opportunity to study a case, it seems fairly certain that oxalated plasma kept at 4 C. in a silicone-coated container will in a few days have a marked depletion of labile factor and will closely resemble the plasma obtained from a patient having a congenital deficiency of the clotting agent. Alexander [24] states that parahemophilic plasma (labile-factor-deficient) is indistinguishable from aged normal plasma as to the rectifying action of fresh plasma on the prothrombin time. When plasma deficient in labile factor is mixed

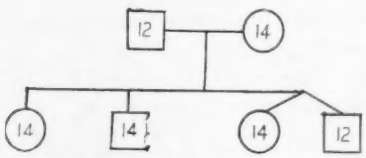


Fig. 5 (Family 6).—Pedigree of stable-factor deficiency.

with an equal volume of fresh plasma from a patient with panhypoprothrombinemia, the prothrombin time is 12 seconds (Fig. 2).

COMMENT

An inextricable association exists between the one-stage prothrombin time and the hypoprothrombinemic states; in fact, a prolonged prothrombin time is the *sine qua non* of every known congenital deficiency of either prothrombin or of the accessory factors. It is therefore of paramount importance to have an understanding as to what is measured by this technically simple test. In analyzing the results of this procedure, it is observed that the prothrombin time in many species is strikingly constant, provided a thromboplastic agent such as acetone-dehydrated rabbit brain is employed. For normal human plasma, it is consistently 12 seconds.

From experimental studies, it has been established with reasonable certainty that the 12-second value is fixed by the concentration of prothrombin but requires at least two other factors, which may be designated as labile and stable. These are in excess normally, but if either drops below a critical level the prothrombin time becomes prolonged. The test under these conditions is no longer a measure of prothrombin but of the deficient factor, either labile or stable. An excess of either, however, does not shorten the prothrombin time; i. e., a lack of prothrombin cannot be compensated by a marked increase of either of the two accessory factors.

A prolonged prothrombin time may be due to a deficiency of prothrombin or of labile or stable factor, provided the thromboplastic reagent employed in the test does not contain these factors as contaminants. Rabbit brain is especially satisfactory as the source of the reagent, since it is nearly bloodless and therefore free of the various plasma clotting factors. A normal prothrombin time, when obtained with this reagent, establishes that the prothrombin concentration is normal and that the labile and stable factors are above the minimal required level. A prolonged prothrombin time, on the other hand, not only establishes a hypoprothrombinemic state but also furnishes a fairly accurate measure of the bleeding potential, irrespective of which of the three basic factors is responsible. Obviously, the indiscriminate use of various types of thromboplastic agents can result in serious errors.

Prothrombin deficiency in man has been particularly confusing, chiefly because the evidence § which strongly supports the concept that prothrombin is present partly free and partly inactive has received little attention and consideration. In adult blood only about 20% of the total prothrombin is in the free state,[20] and it is this fraction alone which determines the prothrombin time. If all the prothrombin were active, the value would be 8 instead of 12 seconds.

§ References 25-28.

Theoretically, three types of hypoprothrombinemia can occur, namely: (1) a lack of both free and inactive prothrombin, (2) a low level of free but a normal concentration of inactive prothrombin, and (3) a normal content of free but an absence of inactive prothrombin. The third type is that found in the blood of newborn infants.[20] Although the total prothrombin is only about 25% of normal, the prothrombin time is normal because the level of the free prothrombin is the same as in adult blood.

The first type, in which a lack of both free and total prothrombin is found, may be designated as panhypoprothrombinemia or hypoprothrombinemia vera. The affected members of Families 1 and 2 illustrate this type of deficiency. One may postulate that the cause is an inability to produce sufficient prothrombin to maintain the normal level. It is fairly well established that the metabolic turnover of prothrombin is amazingly high ‖; nearly all of the circulating prothrombin has to be replenished approximately every 24 hours. Since it has been further found that a low prothrombin level can be brought to normal in less than four hours, it seems reasonable to conclude that the maximum production capacity is six to eight times greater than the rate of consumption. This offers a wide margin of safety and probably accounts for the relative infrequency of hypoprothrombinemia.

In attempting to account for congenital deficiency of prothrombin, it is helpful to consider it on the basis of the concept that prothrombin is synthesized by an enzyme system (ÆK) consisting of an apoenzyme (Æ), a protein presumably produced by the liver, and a prosthetic group (K), supplied by vitamin K.[32] In the panhypoprothrombinemias it seems likely that the apoenzyme is deficient. Since the condition is familial, it is very probable that it is inherited. The finding that the parents of a child with the disease exhibit no abnormality does not gainsay that they may be carriers. They may be heterozygous, having one defective gene that is concerned with the production of apoenzyme. It is conceivable that even if their capacity to synthesize prothrombin is thereby reduced it still may be adequate to maintain the normal level. A person who inherits two defective genes will have such a diminished capacity to synthesize prothrombin that the level of both free and total prothrombin will be low. To establish the correctness of this explanation, more information, especially concerning the transmission of the defect, will be necessary.

The two boys of Family 1 and the girl of Family 2 have a bleeding tendency which clinically is indistinguishable from hemophilia. These children have a slightly prolonged clotting time, and they have had deep-muscle bleeding, hemarthroses, hematuria, and bleeding from cuts, particularly in the mouth and after extraction of teeth. The condition is fairly easily diagnosed. Both the prothrombin time and total prothrombin time are prolonged, which distinguishes the condition from Type II, in which the total prothrombin time is normal. By mixing the patient's plasma with an equal volume of stored human plasma, a normal prothrombin value is obtained, which distinguishes the condition from labile-factor deficiency. The differentiation of true panhypoprothrombinemia and stable-factor deficiency is somewhat more difficult, and until the findings of Alexander, Owren, and Koller on the stable factor were available these two entities could not be separated diagnostically. As will be discussed later, the addition of stable factor or aged serum normalizes the prothrombin in stable-factor deficiency but not in true hypoprothrombinemia.

While panhypoprothrombinemia, or congenital hypoprothrombinemia Type I, is best explained by a lack of the organism's ability to synthesize prothrombin, the condition which is designated as Type II may be accounted for by an abnormality in the mechanism that regulates the level of free or active prothrombin in the blood. It has been postulated that the inactive prothrombin (prothrombinogen) is prothrombin that is blocked either by an actual inhibitor or by a

‖ References 29-31.

molecular change. Whatever the inhibitor is, it may be designated as X. Accordingly, prothrombinogen is prothrombin X. When plasma is stored at 4 C., the inhibitory activity is lost, with the result that the active prothrombin is increased and the prothrombin time therefore becomes shortened. In fresh blood, one may regard the ratio of the free to the inactive prothrombin as being maintained in an equilibrium which is mediated through a Y-factor [33]:

$$\underset{\text{(prothrombinogen)}}{\text{Prothrombin X}} + \text{Y} \rightleftarrows \underset{\text{(active)}}{\text{Prothrombin}} + \text{XY}$$

Little is known concerning the nature of the Y-factor except that it is not adsorbed by agents such as tricalcium phosphate. Its concentration is fixed, which accounts for the constancy of the prothrombin time. Factor Y per se has no direct effect on the prothrombin time; yet it is the actual determinant in fresh plasma, because it fixes the amount of free prothrombin.

The concept of a Y-factor explains the normal prothrombin time obtained when panhypoprothrombinemic plasma is mixed with normal plasma. In such a mixture, the concentration of Y-factor is the same as in normal blood, and since normal plasma furnishes prothrombinogen, enough active prothrombin is formed in the mixture to bring it to the normal level. In R. F.'s plasma a lack of Y-factor occurs; therefore, in a mixture of his with normal plasma, the Y-factor does not become normal and the prothrombin time is prolonged. Until this concept was developed, the prothrombin time of these mixtures was very puzzling and misled one of us (A. J. Q.) in 1947 to call panhypoprothrombinemia a pseudohypoprothrombinemia.[12]

From the study of Family 3 it appears that the concentration of the Y-factor is established by inheritance. The mother with a prothrombin time of 16 seconds transmitted the defect to one son and one daughter, while three sons were normal. Whether the defect is inherited as a dominant cannot be determined from the available data. In the affected members of the family the concentration of free prothrombin is 45% of normal, as calculated from the senior author's prothrombin curve.[33] This value is sufficiently above the hemorrhagic level to make the condition entirely subclinical. Theoretically, it is possible to have a very low concentration of active prothrombin and still have an almost normal total prothrombin. One can only surmise that such persons would have a bleeding tendency, since no such cases have been reported. The characteristic diagnostic findings are (1) the normal total prothrombin value and (2) a prothrombin time longer than 12 seconds when the blood is mixed with an equal volume of normal blood. It is significant that the addition of stable factor partially corrects the prothrombin time in this type of hypoprothrombinemia (Table 1).

The relation of the stable factor to coagulation presents a complicated problem. It seems fairly certain that Factor VII of Koller, proconvertin of Owren, S. P. C. A. of Alexander, and co-thromboplastin of Mann are the same and may justifiably be given the noncommittal name of stable factor. This agent is distinct but closely related to prothrombin both in its physical properties and in its action. When stable factor is diminished the prothrombin time is prolonged and the conversion of prothrombin to thrombin in the two-stage method is slow. Since the concentration in the serum is much higher than in the plasma, it is generally accepted that stable factor exists in a precursor state. Like prothrombin, it is adsorbed by agents such as tricalcium phosphate. Deprothrombinized plasma is therefore devoid of both prothrombin and stable factor.

Congenital lack of stable factor constitutes a clinical entity which appears to be commoner than true congenital hypoprothrombinemia. The prothrombin time measured by the unmodified one-stage test is usually from 30 to 60 seconds. By the addition of a small quantity of serum or a partially purified preparation of stable factor, the prothrombin time can be reduced to normal (11½ to 12 seconds). Significantly, when the total prothrombin time is determined (the prothrombin time of stored plasma) it is found to be

prolonged (18½ seconds, for example, in one patient), but if stable factor is added to the reagents a value of 8 seconds is obtained, the same as in normal blood. This shows that the patient's free prothrombin and prothrombinogen are normal in amounts and that the latter is distinct from stable factor.

Family 4 illustrates succinctly the hereditary pattern of this disease (Fig. 4). Both father and mother have a prothrombin time of 14 seconds, indicating that both are heterozygous in regard to the defective gene. Their daughter apparently received both defective genes and therefore has a marked lack of stable factor and a serious bleeding tendency. Her brother has a prothrombin time of 14 seconds, showing that he is heterozygous. It is probable that if the parents had more children some would be homozygous as to the normal gene and have a prothrombin time of 12 seconds. It is important to note that, with a standardized prothrombin time determination that consistently gives 12 seconds for normal persons, persons who are heterozygous can be detected with ease and certainty. Since a relatively high ratio of the members of a family in which the disease exists are heterozygous, the danger of consanguineous marriages is obvious.

The diagnosis of congenital stable-factor deficiency is essentially one of differentiating it from true hypoprothrombinemia. The following tabulation is useful:

	True Hypoprothrombinemia	Stable Factor Deficiency
Effect of adding stable factor (aged serum) on prothrombin time	None	Will normalize
Prothrombin consumption time	Very prolonged and uncorrected by stable factor	Usually prolonged, but normalized by adding stable factor
Prothrombin time of other members of the family	All normal, including parents	Parents will have a prolonged time, and other members may have

Curiously, the clotting time of patients with a true hypoprothrombinemia is always moderately prolonged, whereas in the two cases of stable-factor deficiency it has been normal. Owren [35] also found that two cases of severe stable-factor deficiency (hypoproconvertinemia) which he studied had a normal or only slightly prolonged clotting time. Hagen and Watson, however, observed a very prolonged clotting time in their patient. While M. P., of Family 4, is a severe bleeder, the condition in H. S., of Family 5, is mild. The prothrombin time of the latter is definitely shorter than that of M. P., which may account for the clinical difference. The case of Desjardins and Droulard,[36] which probably too is stable-factor deficiency, also is characterized by a mild clinical course.

Although the labile factor was discovered in the Marquette laboratory,[9] the authors have had no opportunity to study any patients having labile-factor deficiency. From the studies of others, one can summarize some of the important features of congenital labile-factor deficiency. The report of Brink and Kingsley [37] is particularly helpful. It seems fairly clear that the plasma of such patients closely resembles oxalated plasma stored at 4 C. in a silicone-coated container. When the patient's plasma is mixed with stored plasma, no correction of the prothrombin time occurs, whereas both plasmas are corrected by the addition of fresh plasma, either as such or after being deprothrombinized with tricalcium phosphate.

The clinical findings are not dissimilar from those of other states of hypoprothrombinemia. From the reported cases, it appears that mucous membrane bleeding, such as epistaxis and menorrhagia, is common. This was observed in the first published case (Owren).[10] Brink and Kingsley reported that two affected persons in the family which they studied bled to death at the first menstrual period. The three siblings reported by Alexander and Goldstein [38] had a prolonged bleeding time, which was not observed in the other reported cases.

The hereditary pattern appears to resemble that of stable-factor deficiency. That the condition is congenital and familial is clear from the studies of various workers, and the investigation of Brink and Kingsley throws much light on the mode of transmission. Since their family is large and the possibility of intermarriages fairly strong, it seems very likely that the defective gene is recessive.

Using their symbols "b" as the abnormal and "B" as the normal trait, one may assume that only persons who are "bb" will have a frank hemorrhagic tendency. The disease can only arise if both father and mother are heterozygous (Bb). The distributions will be 1 BB: 2 Bb: 1 bb. It is not clear from their findings whether the heterozygous person has consistently a slightly prolonged prothrombin time. The children of two of the affected members of the family of Brink and Kingsley do, but the parents of the three bleeders have normal prothrombin times. The alternative explanation is that the defect is a dominant gene with variable penetrance. It is desirable that further studies be made to determine the prothrombin time in the carriers.

distinct types of hypoprothrombinemic states exist clinically. All are characterized by a prolonged prothrombin time which, when it exceeds 20 seconds, becomes manifested by a hemorrhagic tendency. The four types can readily be differentiated by relatively simple laboratory methods, particularly by the prothrombin time, the total prothrombin time, and the prothrombin consumption test. Table 3 serves as the guide. By mixing the patient's plasma with an equal volume of normal plasma, a normal prothrombin time is obtained with all except Type II, which is somewhat prolonged. When the plasma is mixed with stored human plasma, a normal prothrombin time will be found if the condition is hypoprothrombinemia of Type I or

TABLE 3.—*Differential Diagnosis of Congenital Hypoprothrombinemic States*

	Congenital Hypoprothrombinemia		Stable-Factor Deficiency	Labile-Factor Deficiency
	Type I	Type II		
Prothrombin time of				
Plasma	Prolonged	Prolonged	Prolonged	Prolonged
Plasma + normal plasma (1:1)	Normal	Slightly but definitely prolonged	Normal	Normal
Plasma + stored plasma (1:1)	Normal	Slightly prolonged	Normal	Prolonged
Plasma + stored serum (9:1)	Prolonged	Prolonged	Normal	Prolonged
Total prothrombin time	Prolonged	Normal	Prolonged	Normal
With stored serum (9:1)	Prolonged	Normal	Normal	Normal
Prothrombin consumption time	Very high	Normal	Normal or prolonged	Very short

The diagnosis of labile-factor deficiency is simple. In normal plasma the concentration of this agent is remarkably constant. On adding one volume of fresh normal plasma to nine volumes of stored plasma having a prothrombin time of 40 seconds or more, one obtains a prothrombin time of 16 to 20 seconds. When labile-factor-deficient plasma is added to stored plasma, little or no correction is obtained. Perhaps the simplest and easiest way to establish labile-factor deficiency is to add fresh deprothrombinized human or rabbit plasma to an equal volume of the patient's plasma. If labile factor is deficient, the prothrombin time of the mixture will be normal.

The present studies as well as those of other investigators establish that at least four

stable-factor deficiency, but no significant correction will be obtained if it is labile-factor deficiency. The total prothrombin time is normal in Type II and in labile-factor deficiency but is prolonged in Type I and stable-factor deficiency. The prothrombin consumption is very high in Type I and very poor in labile-factor deficiency. By these means, a tentative diagnosis can be made and then verified by more specific tests. The two-stage method alone gives misleading results. With it a normal prothrombin value is obtained in Type II hypoprothrombinemia and variable results are obtained in stable- and labile-factor deficiencies, depending on the purity of the reagents used.

It is interesting and significant that hypoprothrombinemia, which only a decade ago

was accepted as a single clinical entity, actually includes four different states. With a more complete understanding, new light is thrown on the complexity of these physiological processes. Thus, two true congenital hypoprothrombinemias exist but their origins are entirely different. In Type I the free prothrombin is low, because, presumably, the body cannot synthesize the substance sufficiently fast to maintain the normal concentration, while in Type II the mechanism which fixes the level of free prothrombin is altered. Particularly significant but still puzzling are the two accessory factors. The observation that prothrombin consumption is very poor when labile factor is deficient but normal when stable factor is lacking suggests that the former acts in an earlier stage in the conversion of prothrombin to thrombin. Perhaps, in that reaction prothrombin becomes changed to an intermediary product which requires stable factor in order to be changed to thrombin. Since the action of stable factor is still uncertain, a specific name such as proconvertin should be withheld until such time as its functions are established.

While no attempt will be made to discuss the actions of the various factors, it should be pointed out that the congenital deficiencies offer a particularly favorable source of information. In the patients studied the defect appears to be limited to the lack of one factor. Thus, the labile factor is normal in the two types of true hypoprothrombinemia and in stable-factor deficiency. Total prothrombin is normal in all but Type I hypoprothrombinemia. One exception to this generalization is that stable factor appears to be somewhat low in Type II hypoprothrombinemia. Whether this indicates that the stable factor may be linked in some way with prothrombinogen is difficult to answer. It is certain that Type II is different from congenital stable-factor deficiency. The prothrombin time of the latter can be corrected by the addition of normal plasma, whereas in Type II it remains prolonged. The Y-factor is normal in all but Type II hypoprothrombinemia.

Although hereditary transmission is not definitely established in all four types of hypoprothrombinemia, it seems reasonably certain that it may be. In stable-factor deficiency the evidence is clear that a bleeder inherits two defective genes, i. e., he is homozygous. If he marries a normal person, none of his children will be bleeders but all will be heterozygous, who in turn will give the trait to half their children. Fortunately, the unmodified test for prothrombin time readily detects the offspring who received the defective trait. Obviously, they should not marry someone who also is heterozygous in respect to this defect. Although this trait is rare, it happened by sheer coincidence that in Family 4 the mother, who is Polish, and the father, who is Slovak, both have the trait, and their daughter received the defective gene from each parent. Without the sensitive test for prothrombin time such heterozygous persons could not be detected; consequently, it would be difficult to establish a definitive hereditary pattern. Labile-factor deficiency appears to have the same hereditary pattern as that of stable factor. The detailed study of an affected family by Brink and Kingsley [87] shows that when members of such a family intermarry a certain proportion of the offspring are bleeders. The hereditary pattern of hypoprothrombinemia Type I is not known, but if it is the same as that of stable-factor deficiency the bleeders of Families 1 and 2 will not transmit the active bleeding disease to their children but all of their children will be heterozygous. Only in Type II does the probability exist that if a person has a sufficient depression of prothrombin to be a bleeder he will have children who are bleeders.

The treatment of congenital hypothrombinemic states can be rationalized on the basis of present knowledge. Vitamin K will not correct the prothrombin time of any of these conditions. One possible exception may be in true hypoprothrombinemia, since natural vitamin K_1 sometimes slightly increases the prothrombin time and may even have a beneficial effect on controlling bleeding. The only means whereby the prothrombin may be temporarily elevated sufficiently to effect hemostasis is by plasma or whole blood

transfusion. In labile-factor deficiency it is necessary that the blood be fresh, since the labile factor disappears during storage. Whether transfusion of serum has advantages over plasma in stable-factor deficiency is not known, but, interestingly, Crockett and his associates [39] reported controlling bleeding after the extraction of six carious teeth with blood and serum in a patient who undoubtedly had stable-factor deficiency.

SUMMARY

Four distinct clinical entities, congenital in origin, are characterized by a prolonged one-stage prothrombin time. Two of these conditions are due to a low free prothrombin concentration. In the first, designated as Type I, the cause appears to be an inadequate capacity to produce prothrombin, while in Type II the mechanism which fixes the ratio of free to total prothrombin is altered. The third hypoprothrombinemic state is caused by a lack of an accessory factor variously designated as stable, proconvertin, Factor VII, S. P. C. A., or co-thromboplastin. The fourth condition is due to labile-factor (proaccelerin, Factor V, or acglobulin) deficiency.

A study of cases representing the first three conditions is reported, with special emphasis on the pertinent laboratory findings, the clinical course, and the hereditary pattern. The differential diagnosis of the hypoprothrombinemic states is outlined, using as the basis the unmodified prothrombin time and simple modifications to make it specific for the three primary factors (true prothrombin, stable factor, and labile factor) that influence the prothrombin time.

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CLINICAL SYNDROMES ASSOCIATED WITH HYPERNATREMIA

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FIVE CASES of hypernatremia (serum sodium levels above 150 mEq. per liter) associated with brain injury were reported by Allott [1] in 1939. Despite numerous subsequent reports, the frequency with which hypernatremia occurs has not been fully appreciated. Nor has our understanding of the mechanisms producing hypernatremia been greatly enhanced.

In the past four years we have encountered over 100 unequivocal instances of hypernatremia (hyperosmolarity) in acutely ill patients. It seems convenient to divide these cases into three general groups, to which we have arbitrarily given descriptive headings. These divisions are based in part on a concept of the mechanism producing the hypernatremia and in part on the clinical syndrome with which the hypernatremia is associated.

Hypernatremia has been said to be the result of severe dehydration. In the experimental subject prolonged water deprivation will not produce significant hyperosmolarity.[2] It is necessary to add marked water loss to achieve this result. In addition, other factors undoubtedly play a role.

I. PRIMARY DESICCATION SYNDROME

Rapaport [3] has reported in detail the hypernatremia of six infants who had entered the hospital with fever and mild diarrhea of several days' duration. Similarly, we have encountered 15 cases, all of infants under 2 years of age. In all instances the diarrhea was mild, usually consisting of five or six loosely formed stools a day. Temperatures ranged from 102 to 104 F., rectally. Listlessness, irritability, and dehydration formed a constant triad. In only one instance was stool culture revealing. Data on this group of patients are summarized in Table 1. The following is a typical case.

CASE 3.—E. J., a 9-month-old Negro boy, was admitted to the Cook County Hospital on May 20, 1952, with the complaints of diarrhea (five to six loosely formed stools per day), listlessness, and irritability for the past 72 hours. The patient's three siblings were well. Physical examination revealed a 17 lb. (7,710 gm.) dehydrated infant with a temperature of 103.6 F., rectally. No evidence of respiratory infection could be found. Wet eczematous lesions were noted on the perineum.

Shortly after admission the child had a mild convulsion and was given 30 mg. phenobarbital. Serum chemical analysis at this time revealed the following: sodium, 166, and chloride, 131 mEq. per liter. Stool cultures were negative. In the next 48 hours the child received 1,500 cc. of 5% dextrose in water intravenously and approximately 500 cc. of nonsaline fluid orally. During this period the diarrhea receded. The serum sodium and chloride dropped to 151 and 124 mEq. per liter, respectively. During the next 48 hours the patient was taking fluids by mouth well. The diarrhea had subsided, and the fever abated. At this time the serum electrolytes had returned to normal ranges. He was discharged as well 11 days after admission.

All but one of these 15 patients recovered (Table 1). Electrolytes returned readily to normal values after administration of adequate amounts of salt-free fluids. The patients' clinical condition as well as the diarrhea seemed to parallel the restitution of the serum electrolytes to normal values.

Comparable, at least in response to therapy, is a group of patients, usually elderly, whose underlying disease precludes their adequately caring for themselves. Hypernatremia may develop in such a patient even while in the hospital, especially during excessively hot weather or during a particularly toxic episode. The following are abstracts of two illustrative cases.

R. E., a senile Negro man whose age was estimated at 75, entered the hospital on July 2, 1953.

From the Hektoen Institute for Medical Research and the Departments of Medicine, Cook County Hospital and the University of Illinois College of Medicine.

The patient was confused and disoriented, and no history was obtainable. Blood pressure was 140/90; pulse rate, 72, and temperature, 100 F. No significant physical findings were elicited. Blood nonprotein nitrogen was 50 mg. per 100 cc.; serum sodium, 138, and serum chloride, 102 mEq. per liter. Nine days after admission and after several days of extremely hot weather, the patient was noted to be dehydrated, stuporous, and moderately tachypneic. Fine rales were present in the right base. Temperature was 101 F., rectally. Serum chloride was 122, and sodium, 160 mEq. per liter; blood NPN, 76 mg. per 100 cc.; blood creatinine, 2.8 mg. per 100 cc., and total protein, 8.1 gm. per 100 cc. Antibiotic therapy was instituted, and 4,000 cc. of 5% dextrose in water was given intravenously in the next 24 hours, after which the patient was more alert and appeared less toxic. The serum sodium and chloride were reduced to 151 and 110 mEq. per liter, respectively. In the next 24 hours the patient received 2,000 cc. of 5% dextrose in water intravenously and approximately 1,000 cc. of salt-free fluids orally. Following this the serum electrolytes were within normal range. The blood NPN was 50 mg. per 100 cc. The patient appeared to be restored to his previous state.

T. R., a 20-year-old Negro woman, was admitted to the hospital in a semicomatose state. She responded to stimuli but was disoriented. Temperature was 104.6 F., rectally; respiration rate, 30, and pulse rate, 110. Microlymphadenopathy, questionable splenomegaly, and reduplicated apical first heart tones were the significant findings. Serum electrolytes on admission were as follows: sodium, 169, and chloride, 124 mEq. per liter. The blood NPN was 65 mg. per 100 cc.; creatinine, 2.4 mg. per 100 cc. The patient received 4,000 cc. of 5% dextrose in water intravenously and approximately another 1,000 cc. of water orally in the next 24 hours. At the end of this time, serum electrolytes had returned to normal ranges but there was little improvement in the patient's clinical condition. The Hargraves phenomenon for lupus erythematosus was demonstrated, and the patient was started on intravenous corticotropin (ACTH), to which she made a good clinical response.

We have encountered 18 cases of this nature. At the time of the hypernatremia these patients present a clinical picture characterized by dry skin, moderate tachypnea, torpor or stupor, moderate to marked hyperthermia, and, occasionally, muscular irritability. Localizing neurologic signs are absent. In addition to the elevation of the serum sodium and chloride, moderate elevation of the blood NPN invariably occurs. This rarely exceeds 100 mg. per 100 cc. It is accompanied by a slight but not comparable rise in the blood creatinine, to levels rarely exceeding 3.5 mg. per 100 cc. The serum potassium is inconstant. It is usually of high normal range but occasionally is even lower than normal, a finding which would indicate that the previous loss of water was accompanied by excessive losses of potassium.

The serum electrolytes are readily restored to normal upon the administration of adequate amounts of water. This usually requires a minimum of 3 liters (frequently, in adults, as much as 7 liters). Death occurred in six instances (33%) after the restitution to normal of the serum electrolytes. The

TABLE 1.—*Infants with Diarrhea*

Case	Sex	Age	Sodium, mEq./L.	Chloride, mEq./L.	Potassium, mEq./L.	Bicarbonate, mEq./L.	Nonprotein Nitrogen, Mg./100 Cc.	Remarks
1	F	21 mo.	152	120	...	17	41	Recovered
2	M	4 mo.	169	135	2.2	..	60	Died
3	M	9 mo.	166	131	3.1	4	66	Recovered
4	M	11 mo.	156	131	...	6	52	Recovered
5	M	1 mo.	154	130	4.4	5	..	Recovered
6	F	4 mo.	175	138	5.3	..	78	Recovered
7	F	12 mo.	151	128	...	5	96	Recovered
8	F	2 wk.	154	124	4.1	4	52	Recovered
9	M	12 mo.	154	119	2.8	10	60	Recovered
10	F	9 mo.	151	120	5.3	11	58	Recovered
11	F	8 mo.	171	141	5.6	..	54	Recovered
12	F	6 wk.	153	128	...	5	..	Recovered
13	M	2 mo.	155	126	4.2	6	50	Recovered
14	M	16 mo.	153	124	3.0	..	60	Recovered
15	M	9 mo.	174	142	5.8	9	78	Recovered

prognosis is that of the underlying disease if it can be assumed that the hypernatremia has not persisted long enough to produce irreversible brain damage. Since the hypernatremia in some surviving patients is known to have lasted at least 48 hours, it appears unlikely that in humans irreversible brain damage occurs in less than 48 to 72 hours. In none of the three patients in whom postmortem examinations were made was significant brain damage found.

II. CENTRAL NERVOUS SYSTEM INJURY

Four of the five cases of hypernatremia reported by Allott [1] came to necropsy. All showed severe brain damage. In 1943, Leutscher and Blackman [4] described five patients who developed hypernatremia during the course of what in the light of our present knowledge must be assumed to have been renal tubular necrosis secondary to sulfonamides. Postmortem examination on two of these patients showed, in addition to renal changes, edema, gliosis, and petechial hemorrhages in the brain. Goodale and Kinney,[5] in 1949, reported a similar case. Peters [6] has reported the development of hypernatremia in a patient subsequent to surgery for a craniopharyngioma. MacCarthy and Cooper [7] were forced to ligate both anterior arteries during the removal of a mixed pituitary adenoma. The patient developed sustained hypernatremia and died. Postmortem examination revealed no renal pathology. The brain showed extensive infarction, hemorrhage, and edema. These authors also reported two other cases of hypernatremia.[8] One patient had a massive cerebral hemorrhage; the other, a pituitary adenoma. Higgins and co-workers [9] reported five cases of hypernatremia in patients who had suffered severe trauma. All five patients died. Postmortem examination revealed extensive brain damage in all five. None, however, showed significant renal lesions.

Sixty-three patients with acute hypernatremia secondary to intracranial pathology have been seen at this hospital in the past four years (Table 2). In the great majority of cases the lesion was encephalomalacia and hemorrhage. However, hypernatremia has also occurred subsequent to cerebral lacerations, subdural hematoma, subarachnoid hemorrhage, metastatic and primary malignant disease, and meningitis (tuberculous and nontuberculous). All these patients entered the hospital in coma or semicoma; localizing neurologic signs were usually absent, although anisocoria and/or ophthalmoplegia were noted in approximately 10% of the cases. In five cases (Cases 7, 8, 11, 20, and 31, Table 2) glycosuria and acetonuria were present on admission and the coma was falsely ascribed to diabetic acidosis. In these instances, the patients were treated with saline solutions because the marked hypernatremia which was already present was unrecognized. Absence of tachycardia and of Kussmaul breathing, presence of adequate blood pressure, anisocoria and/or ophthalmoplegia, and a moist skin, are all findings which should alert the physician to the possibility that the cause of coma may be intracranial pathology rather than diabetic acidosis. In such cases the ketosis is probably due to starvation. The following case is presented to illustrate the findings typical of this group of patients and the possibility of confusion with diabetic acidosis.

CASE 11.—J. M., a 48-year-old Negro man, was admitted on April 17, 1952. He was stuporous, and no history was obtainable. The blood pressure was 114/90; pulse rate, 92; respiration rate, 18, and temperature, 100.6 F., rectally. The left pupil was dilated, and the left eye deviated to the right. No other significant findings were elicited. The urine showed acetone, 4+; specific gravity, 1.002; albumin, 4+, and reducing substances, 4+. The patient was given 100 units of regular insulin subcutaneously. Isotonic sodium chloride solution, 1,000 cc., was started by intravenous drip. This was followed by 250 cc. of 6 M sodium lactate and 1,000 cc. of 5% dextrose in isotonic sodium chloride solution. Five hours after admission urinalysis revealed 2+ reducing substances and a trace of acetone. Chemical analysis of blood, drawn before therapy was instituted, showed the following: serum sodium, 168; chloride, 126, and bicarbonate, 20 mEq. per liter; glucose, 600 mg. per 100 cc.

In the next 24 hours the patient received 4,000 cc. of 5% dextrose in water, after which the serum sodium was 168 and chloride, 124 mEq. per liter. The blood glucose was 248 mg. per 100 cc. In the next 24 hours the patient received another 4,500 cc.

TABLE 2.—*Hypernatremia Associated with Lesions of Central Nervous System*

Case	Age, Yr.	Sex	Sodium, mEq./L.	Chloride, mEq./L.	Potassium, mEq./L.	Bicarbonate, mEq./L.	Nonprotein Nitrogen, Mg./100 Cc.	Creatinine, Mg./100 Cc.	Diagnosis	Remarks
1	74	F	156	126	3.8	10	196	6.4	Encephalomalacia	Salmonellosis
2	65	M	154	119	...	16	...	...	Encephalomalacia	No localizing signs
3	42	F	169	129	5.4	..	93	4.3	Carcinoma, breast	4+ reducing substances, anisocoria
4	86	M	163	119	4.6	25	122	...	Carcinoma, bladder	Metastasis to brain
5	70	M	160	130	...	..	130	4.6	Encephalomalacia	Extensive hemorrhage
6	50	M	154	118	2.3	18	...	...	Cerebral laceration	Traumatic
7	53	M	157	128	4.1	20	76	2.3	Encephalomalacia	4+ reducing substances, 4+ acetone
8	73	M	154	125	...	17	104	4.5	Encephalomalacia	4+ acetone, 4+ reducing substances
9	70	M	157	120	...	..	76	2.8	Encephalomalacia	No localizing signs
10	69	F	160	124	5.1	..	...	...	Encephalomalacia	Anisocoria, spinal fluid grossly bloody
11	48	M	168	126	5.6	20	186	5.2	Encephalomalacia	4+ reducing substances, 4+ acetone, anisocoria
12	76	M	157	113	4.8	..	...	...	Encephalomalacia	Pathologic reflexes; recovered
13	63	F	153	121	4.2	21	158	3.4	Encephalomalacia	Left hemiplegia, 1+ acetone
14	81	M	155	120	...	..	57	1.6	Encephalomalacia	No localizing signs
15	66	M	154	114	5.0	..	...	...	Polioencephalitis of Wernicke	No localizing signs
16	58	M	157	124	...	12	...	...	.....	.....
17	42	M	169	128	3.4	..	106	3.6	Encephalomalacia	Right facial, anisocoria
18	68	M	172	132	3.2	22	72	1.7	Carcinoma, esophagus	Aphasia, metastasis to brain
19	66	F	160	128	4.5	18	60	...	Encephalomalacia	Right hemiplegia
20	76	M	170	126	4.6	..	178	4.6	Encephalomalacia	3+ reducing substances, 1+ acetone
21	72	F	152	121	4.4	17	171	3.2	Encephalomalacia	No localizing signs
22	82	F	157	120	5.1	16	107	1.6	Encephalomalacia	No localizing signs
23	67	M	167	137	6.6	8	238	6.5	Encephalomalacia	No localizing signs
24	87	M	178	141	4.6	..	196	7.5	Encephalomalacia	Cheyne-Stokes respiration
25	73	F	169	131	4.0	9	...	...	Encephalomalacia	No localizing signs
26	49	F	166	124	2.2	..	56	...	Encephalomalacia	Left hemiplegia
27	71	F	160	120	3.8	23	53	...	Encephalomalacia	No localizing signs
28	60	F	152	120	3.1	19	54	1.7	Meningitis	Temperature 105.6 F., rectally
29	81	M	166	139	4.8	9	180	6.2	Carcinoma, prostate	Metastasis to brain

30	70	M	152	116	5.1	18	53	...	Encephalomalacia	Pathologic reflexes present
31	71	F	168	126	5.0	27	145	5.2	Encephalomalacia	4+ acetone, 4+ reducing substances
32	64	M	151	124	...	..	238	6.5	Encephalomalacia	No localizing signs
33	44	F	152	116	4.0	..	...	...	Meningitis	Temperature 106.2 F., rectally
34	52	F	157	119	3.0	18	98	2.1	Meningitis	Infected burns
35	63	F	170	126	...	..	...	...	Encephalomalacia	Right hemiplegia
36	82	F	169	121	4.6	..	204	5.0	Encephalomalacia	No localizing signs
37	73	M	160	111	5.0	26	200	4.8	Encephalomalacia	No localizing signs
38	76	M	169	133	4.4	18	68	1.9	Encephalomalacia	No localizing signs
39	53	M	160	115	...	21	100	2.1	Bronchogenic carcinoma	Metastasis to brain
40	24	M	169	132	5.1	..	...	...	Encephalomalacia	No localizing signs
41	67	M	162	118	4.6	23	184	6.4	Subdural hematoma	Trauma
42	70	F	173	135	5.4	16	168	4.5	Meningitis	Lobar pneumonia
43	68	M	156	117	3.6	19	...	...	Encephalomalacia	Right hemiplegia
44	78	M	165	131	4.2	17	140	3.8	Encephalomalacia	No localizing signs
45	54	M	155	120	3.6	..	...	...	Encephalomalacia	No localizing signs
46	77	M	152	120	4.0	..	59	2.0	Encephalomalacia	Previous hemiplegia
47	78	F	157	119	3.3	..	50	...	Encephalomalacia	Ophthalmoplegia, right
48	53	F	154	120	3.2	15	82	5.4	Encephalomalacia	4+ reducing substances
49	65	M	159	124	5.5	16	57	1.8	Encephalomalacia	Anisocoria
50	22	M	160	122	4.0	24	55	1.8	Subdural hematoma	Recovered
51	35	M	154	119	3.8	..	50	...	Subarachnoid hemorrhage	Anisocoria, recovered
52	67	M	153	128	3.7	15	42	...	Meningitis	Jaundice
53	62	M	157	135	3.1	..	40	...	Encephalomalacia	No localizing signs
54	56	F	152	122	4.2	14	126	3.0	Encephalomalacia	4+ reducing substances, anisocoria
55	55	F	157	119	4.0	..	88	1.6	Encephalomalacia	Anisocoria
56	64	F	154	119	5.4	15	78	4.1	Encephalomalacia	No localizing signs
57	54	M	166	130	5.6	..	148	4.4	Encephalomalacia	No localizing signs
58	62	M	178	...	4.2	16	126	3.6	Carcinoma, lung	Metastasis to brain
59	32	M	163	126	5.5	20	185	6.5	Meningitis	Miliary tuberculosis (culture)
60	[illegible]	M	165	122	5.0	17	180	5.0	Meningitis	Pulmonary tuberculosis
61	67	M	162	145	5.5	13	171	5.0	Encephalomalacia	Temperature 105.4 F. terminally
62	76	M	169	122	6.0	16	222	8.5	Encephalomalacia	No localizing signs
63	45	M	165	145	3.5	8	82	2.3	Meningitis	Pulmonary tuberculosis

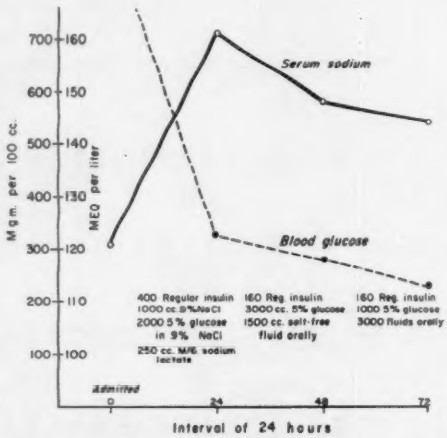
of 5% dextrose in water; serum sodium was then 157, and chloride, 116 mEq. per liter. Intravenous infusions of 5% dextrose in water were continued. The patient remained comatose, and his temperature rose to 105.4 F., rectally. Approximately 60 hours after admission the patient died.

Despite the restitution of isotonicity, which in these patients is extremely difficult, terminal hyperthermia and death are the rule, usually within 48 to 72 hours. Necropsy in this group of patients invariably revealed some gross or microscopic brain injury. The findings varied from edema, moderate gliosis, and petechiae to massive encephalomalacia with hemorrhage.

An additional 17 patients entered the hospital in coma without localizing signs. These patients died soon after admission, before any definite diagnosis could be established. The laboratory results frequently were not available before the patient died. Hypernatremia (hyperosmolarity) of the order of magnitude described above was the rule. Postmortem examinations in seven of these patients revealed brain damage varying from simple edema with petechiae to extensive cerebral lacerations. It is probable that many, if not all, of these patients also represent instances of hypernatremia subsequent to intracranial lesions. However, the clinical data available are so meager that they are described separately.

III. DIABETIC COMA AFTER THERAPY

Danowski and his colleagues [10] have called attention to the development of hypernatremia in patients in diabetic coma when they are treated solely with insulin and salt solution. We have encountered nine examples of this phenomenon. In each of our cases, the patient was semicomatose or comatose on admission, was treated with insulin and salt solution, and developed hypernatremia (hyperosmolarity) within the first 24 hours. During the period of hypernatremia the patient's sensorium usually remained somewhat clouded. Restitution of isotonicity rarely took more than 48 hours after appropriate therapy with salt-free fluids was instituted. Frequently it was accomplished within 24 hours. The Figure illustrates the relationship of the serum electrolytes to the glucose level and to the duration of therapy in a typical case. All nine of our patients recovered, their subsequent course being that expected of a diabetic. It is no doubt true that a rise in serum sodium will occur in all patients in diabetic coma who are treated only with insulin and saline solution, and it is therefore advisable, as Peters has long advocated, to use some glucose in water early in the management of these cases. However, it is worthwhile to point out that nine cases of hypernatremia represent a small portion of the total number of patients in diabetic coma treated in this manner at this hospital.



Hypernatremia in diabetic acidosis after therapy with isotonic sodium chloride solution and insulin.

COMMENT

Since even prolonged water deprivation will not, in the experimental subject, produce hypernatremia of the magnitude seen in these cases, additional factors must be operative. In the elderly patient, unable to care for himself, these factors are not difficult to imagine. His incapacitation precludes adequate oral water intake and predisposes to hypostatic pneumonia. The resulting hyperthermia and tachypnea markedly increase the insensible water loss. Such losses are increased during severely hot weather. Furthermore, these elderly patients may be assumed to have degenerative vascular changes in their kidneys,

limiting their concentrating power. To all this is occasionally added water loss through Levine suction, vomiting, or diarrhea. These combinations of circumstances, as well as the rapid response to replacement therapy with water, indicates that these patients truly represent a "desiccation syndrome."

On the other hand, the picture is not so convincing in the case of infants. Severe dehydration in infants secondary to fulminant diarrhea is frequently seen in this hospital. Such patients almost invariably present a severe hyponatremic rather than hypernatremic acidosis. It must be assumed that were it not for the sodium loss in the stools the hypernatremia would be even more severe than is actually observed. The difference between the infants who present hyponatremic acidosis and those who present hypernatremic acidosis is usually the mildness of the diarrhea and the absence of shock in the latter group. One may postulate that the fulminant diarrhea permits so great a sodium loss as to preclude the development of hypernatremia, especially when the shock has resulted in diminished renal blood flow and therefore no significant renal water loss. While these postulations would appear to explain the seeming contradiction in these two groups of patients, they remain to be proved.

It is conceivable that the infantile hypernatremia group represents some form of encephalopathy, of which the mild diarrhea is a manifestation. In only one instance was a causative organism isolated from the stools of these patients. This postulation would then place this group in the category of acute intracranial pathology. Such reasoning is consistent with the data of Finberg and Harrison,[11] * who, in their preliminary report on hypernatremia in 88 infants, found neurological symptoms which in a number of instances were not reversed by restoration of normal serum electrolyte concentrations. These authors, however, point out that in some instances the hypernatremia antedated the neurological manifestations. This would suggest the possibility of the establishment of a vicious circle, which may be initiated either by hypernatremia or central nervous system injury and perpetuated by the other. If this mechanism is operative, it further emphasizes the importance of prompt therapy.

Most workers who have reported cases of acute hypernatremia associated with intracranial lesions have suggested, as the mechanism, the production of acute diabetes insipidus. Since the patient is comatose, he cannot make up his renal loss with oral intake. Experimentally it has been shown that interruption of the supraopticohypophyseal tract at its origin or anywhere in its course through the hypothalamus will produce diabetes insipidus. Lesions of the hypothalamus in close proximity will produce hyperglycemia and glycosuria. The simultaneous occurrence of hypernatremia and hyperglycemia in patients with acute intracranial injury is in accord with the postulation of an acute diabetes insipidus. Chronic hypernatremia has been reported in a patient with diabetes insipidus.[12] This was correctable with vasopressin injection, U. S. P. (Pitressin) and water. Moreover, the difficulty one has in restoring isotonicity in these patients suggests continued excessive losses. On this point it must be mentioned that polyuria is not a feature of this syndrome when seen in the hospital, despite the administration of as much as 5 liters of water in 24 hours. Nor is the hypernatremia rapidly influenced by that degree of therapy. However, we have reason to believe from preliminary tracer studies that the water loss may be as great as 40 to 50% of the total body water.† If these findings can be confirmed, the ineffectiveness of a few liters of fluid can be well understood.

While the cases reported by Leutscher and Blackman [4] and Goodale and Kinney [5] were cited earlier as examples of hypernatremia secondary to acute intracranial injury, the possibility of a primary renal disturbance

* Drs. Finberg and Harrison allowed us to examine the unpublished manuscript.

† Studies on sulfate and antipyrine space in several of these patients were made by Drs. L. Bernstein and R. Ryan, Department of Medicine, University of Illinois College of Medicine.

must be acknowledged. In the diuretic phase of "lower nephron nephrosis" a situation comparable to diabetes insipidus may exist insofar as the kidney has lost its concentrating power. It may well be that this renal diabetes insipidus is the more important mechanism leading to hyperosmolarity in such cases. We have encountered four cases which do not clearly fall into any of the three general categories. In two of these "lower nephron nephrosis" existed.

The adrenal corticosteroids, by promoting water diuresis and enhancing the retention of sodium, may also contribute to the development of hypernatremia. However, hypernatremia of this magnitude cannot be produced in experimental subjects by the administration of these agents.

Peters ‡ has suggested an ingenious explanation of the hypernatremia developing in patients with diabetic acidosis treated with insulin and saline solution. He postulates that the high extracellular glucose level makes the extracellular fluid hypertonic. Water, therefore, leaves the cells for the extracellular compartment. This dilutes the electrolytes, and thus the patient presents a hyponatremic, hypochloremic acidosis.

In these patients this hyponatremia is more virtual than real, since it is due partly to real loss of sodium in the urine and partly to the dilution by water from the cells. When the patient is given insulin, the extracellular glucose concentration falls. Glucose is no longer osmotically effective, and water returns to the cells. The extracellular compartment is thus concentrated, and hypernatremia appears. Administration of sodium chloride or lactate, as well as the promotion of diuresis, only aggravates the situation.

There is considerable inferential evidence to support this hypothesis of Peters. The hypernatremia occurs when the blood sugar is lowered, while in case of hypernatremia secondary to acute intracranial injury the hyperglycemia, when it occurs, is present at the time of the hypernatremia. Preliminary tracer studies have shown such a diabetic patient to have lost approximately 20% of the total body water. However, the calculated intracellular water at the time of hypernatremia was almost identical with the calculated intracellular water at the time of rehydration and restoration to isotonicity. In short, while in the rehydrated patient the total body water was increased by approximately 20% the calculated intracellular water hardly changed. This evidence, if it can be confirmed, would corroborate Peters' hypothesis.

While throughout this paper the discussion has concerned itself with the rise in serum sodium, it must be pointed out that a parallel rise in chloride occurs. Indeed, it may be assumed that in those instances in which the alkali reserve is diminished (e. g., infantile diarrhea) the lowering may be accounted for by a rise of chloride parallel to that of sodium accompanied by a greater loss of sodium than of chloride in the stools.

‡ In Duncan.[18]

SUMMAY

Over 100 cases of acute hypernatremia have been seen in this hospital in the last four years.

With few exceptions these cases all seem to fall into three categories, which we have designated as primary desiccation, central nervous system injury, and diabetic coma after saline therapy.

Hypernatremia may result if patients in diabetic coma are treatly solely with insulin and saline solutions.

The treatment of hypernatremia is the intravenous or oral administration of nonsaline fluids. Such treatment is usually successful except in cases of central nervous system injury severe enough to produce death.

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ACETAZOLEAMIDE (DIAMOX) DIURESIS

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With the Technical Assistance of Neil Reznikov, M.D.; Archie Leder, M.D., and Belle Ruskin, M.S.

THE MECHANISMS by which diuretics exert their effects are probably as various as the drugs themselves. Thus, mercurials have been shown to have direct, nonhemodynamic, effects on the convoluted tubules of the kidney, interfering with reabsorption of chloride, sodium, and, consequently, water. Potassium excretion after mercurials depends more upon body stores, and it is increased by high water and low sodium (reabsorption competition) loads. Moreover, if energy, released perhaps by breakdown of high-energy phosphate bonds, is required for renal tubular reabsorption, inhibition of the activities of enzymes such as adenosine triphasphatase [1] and succinic dehydrogenase [2] shown by mercurials may help to explain their effect. Histochemically, this inhibition has even been localized in the proximal convoluted tubules,[3] although the obligatory energized reabsorption presumably occurs in the distal tubules.

Xanthine, e. g., aminophylline, diuresis parallels and augments that of mercurials, but its exact mechanism, while also largely unconnected with changes in renal blood perfusion, has not been worked out.

Since the report by Schwartz [4] in 1949 of the diuretic effect of sulfanilamide in congestive heart failure, among derivatives preeminent in this regard was found 2-acetylamino-1, 3, 4-thiadiazole-5-sulfonamide (acetazoleamide; Diamox). The less active sodium carzenide sodium *p*-carboxybenzene sulfonamide (Figure) shares with acetazoleamide the probably responsible SO_2NH_2 group.

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Supported in part by a grant from Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

The following acetazoleamide study was concerned with the kind, degree, and length of diuresis; comparison of single and multiple dosage; possible hemodynamic mechanisms; possible effects on enzymes other than carbonic anhydrase, and possible mutual interference with sulfonamide drugs (sulfisoxazole; Gantrisin). Data on the latter will be reported elsewhere.[5]

MATERIALS AND METHODS

Fifteen patients in heart failure originally received from 3 to 6 gm. of acetazoleamide by mouth in divided doses for 24 hours. These patients were all on maintenance doses of digitalis, a 500 mg. sodium diet, fluid intakes of 1,500 to 2,000 cc. daily, and no diuretics for some days prior to the tests. The urinary volumes, sodium, and potassium were determined for two or three 24-hour periods, before, during, and frequently after the administration of the drug. In many instances the serum chlorides, nonprotein nitrogen, sodium, potassium, and CO_2-combining power were determined at various times before and after the use of acetazoleamide. The weights and 24-hour urinary volumes were followed in some instances for as long as three weeks.

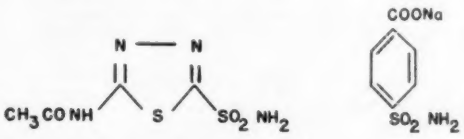
In 12 cases of congestive heart failure on similar regimens a single 500 mg. dose of acetazoleamide was administered at 6 a. m. for the purpose of comparing both the 24-hour and the 8-hour (6 a. m. to 2 p. m., 2 p. m. to 10 p. m., and 10 p. m. to 6 a. m.) urinary excretions before and after acetazoleamide. In 11 of these 12 patients, acetazoleamide was administered, 500 mg. each dose, at 6 a. m., 2 p. m., 10 p. m., and 6 a.m., either one week before or one week after the single-dose experiments. Again, urinary volumes, sodium and potassium excretions, and, frequently, chloride, pH, and serum electrolyte determinations were made both in the 8- and in the 24-hour periods. Two patients without cardiac disease were also utilized in this comparative study.

In 5 patients without heart disease and 6 cases of cardiac failure, renal clearances were done by the mannitol and the *p*-aminohippurate methods, for two 15-minute periods before and four 15-minute periods after 250 mg. of acetazoleamide intravenously. The same 15-minute samples of urine were also available for the study of electrolytes and pH. Blood samples were also obtained for hematocrit

and electrolyte determinations, to learn the acute effects of acetazoleamide.

Relative stroke volume (aortic blood propulsion) estimations at frequent intervals for one hour after 250 mg. of acetazoleamide intravenously were made from ballistocardiograms in four patients without heart disease, four cases of compensated valvular disease, and four cases of cardiac failure. Successive blood pressures, pulse rates, venous pressures, and, in some instances, circulation times (1 gm. of $MgSO_4$) were often obtained simultaneously.

Finally, determinations of adenosine triphosphatase and succinic dehydrogenase activity in some 20 rat hearts and kidneys were done both in vitro and in vivo (one hour after intraperitoneal injection). Histochemical demonstrations of succinic dehydrogenase activity in rat kidneys was also accomplished * from 4½ to 53 hours after acetazoleamide, 100 to 1,250 mg. per kilogram single doses (9 rats) and 40 mg. per kilogram daily for two weeks (5 rats), subcutaneously, and in in vitro experiments (5 to 125 mg. per 20 ml. incubation medium).



Structural formulas of 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide (acetazoleamide; Diamox) (left) and sodium carzenide (sodium *p*-carboxybenzenesulfonamide; Dirnate) (right).

RESULTS

Large Doses.—Table 1 shows the urinary effects of 3 to 6 gm. of acetazoleamide administered in divided doses over 24 hours by mouth in 15 patients with cardiac failure. Urine volume generally more than doubled in 24 hours, with marked rises in sodium and potassium excretion. While the diuresis slackened the day after the drug was given, electrolytes continued to be excreted in large amounts. It is noteworthy that, while diuresis was a constant effect, the urinary sodium and potassium concentration actually fell slightly in 5 and 2 of the 15 cases, respectively, on the first, but not on the second, day. The toxic effects were mild parasthesias and drowsiness, nausea, and vomiting in three cases and a reversible psychosis in one case of nephrosclerosis with uremia (NPN unchanged at 100 to 110 mg. per 100 cc.).

* Dr. Edward Rennels, Department of Anatomy.

Two patients with cirrhosis with ascites tolerated the drug well. In three cases of congestive failure refractory to mercurials acetazoleamide produced a satisfactory diuresis. This dosage was used before it was realized that smaller doses a day or more apart were also effectively diuretic.

In many of the above patients diuresis and weight loss continued for many days (Table 2), up to three weeks, without further use of diuretics. Blood NPN, if elevated, often fell as heart failure receded. Urinary pH generally increased to 8, and as high as 9.6, the first and often the second day after drug administration. In some instances there was a rebound fall in urinary pH the second day, as low as 4.8. The CO_2-combining power fell less than 10%, never below 40 mEq. per liter, even in cases of cor pulmonale heart failure. The serum pH never fell below 7.2.

The following case of severe congestive failure due to cor pulmonale is instructive in this regard.

L. T., a 28-year-old Negro woman, No. 5722K, was admitted to John Sealy Hospital April 30, 1954, with the diagnosis of chronic bronchial asthma (since age of 9), status asthmaticus, recent bronchopneumonia, and cor pulmonale with heart failure, Class IV. Marked right heart dilatation was noted roentgenographically and electrocardiographically. Digitalization induced ventricular ectopic beats, with bigeminy, and dyspnea and failure signs persisted despite aminophylline, antibiotics, mercurials, croup tent, intermittent oxygen under pressure, and nebulizers. On the contrary, the CO_2-combining power rose in six days from 69.2 vol. % to 92.8 vol. %, and coma supervened. With the patient placed in a respirator, the CO_2-combining power fell within five to six days to 82.4 vol. %, with some improvement, but sleepiness and muscle cramps continued. Acetazoleamide was then started in divided doses, 250 and then 500 mg. daily. Within 24 hours the CO_2-combining power was down to 63.6%, and it remained at about that level for the next two weeks. There was a 13% body weight (fluid) loss one week prior to acetazoleamide administration, 17% loss the first week of the use of acetazoleamide, and gradual regaining of 6% of the body weight during the following two weeks. The respirator could be discontinued five to six days after the beginning of acetazoleamide administration.

TABLE 1.—*Results of Oral Administration of Three to Six Grams of Acetazoleamide in Divided Doses over Twenty-Four Hours in Fifteen Cases of Congestive Heart Failure*

	Urine Volume, % Change *	Urine Sodium, mEq./L., % Change *	Urine Potassium, mEq./L., % Change *	Body Weight, % Change *
First day (drug)	+128	+ 82	+63	−1.6
Second day (no drug)	+ 73	+165	+99	−3.3

* Per cent change from 24-hour control values.

TABLE 2.—*Results of Single and Multiple Doses of Acetazoleamide in Patient W. A.*

Days	Urine Volume, % Change *	Urine Sodium, % Change	Urine Potassium, % Change	Body Weight, % Change
1st	− 64	.....	.....	.....
2nd	− 27	.....	.....	.....
3rd	+ 3	.....	.....	.....
4th †	− 3	.....	.....	.....
5th	+ 40	+460	+12	− 1.4
	(6−2 +4 | 2−10 +76 | 10−6 +44) ‡	(6−2 +267 | 2−10 +330 | 10−6 +992)	(6−2 +24 | 2−10 0 | 10−6 +29)	....
6th	+ 74	+133	− 2.6	− 2.6
7th	− 15	+262	− 3.6	− 3.6
8th	− 14	+446	− 4.3	− 4.3
9th	+ 42	+270	− 5.7	− 5.7
10th	+122	+353	− 7.9	− 7.9
11th §	+130	+525	−12.8	−12.8
12th	+ 58	+530	+34	−14.7
	(6−2 +93 | 2−10 +87 | 10−6 +14)	(6−2 +475 | 2−10 +388 | 10−6 +841)	(6−2 +35 | 2−10 +18 | 10−6 +55)	....
13th	+150	+820	+35	−18.4
14th	+ 34	+ 64	+ 2	−19.3

* Per cent change from control values considered as 0%.
† Single dose, 500 mg. acetazoleamide, given on the fourth day.
‡ In parentheses are shown per cent changes for eight-hour periods. All other values are for the 24-hour period
§ Multiple doses, 500 mg. every eight hours for four doses, given on the eleventh day.

TABLE 3.—*Eight-Hour Results of Oral Administration of Acetazoleamide, 500 Mg. Once (Ten Cases) or Four Times (Eleven Cases) in Twenty-Four Hours, in Cases of Congestive Failure and in Two Patients Without Heart Disease*

		% Change After One 500 Mg. Dose Acetazoleamide, No. of Patients			% Change After Four 500 Mg. Doses Acetazoleamide, No. of Patients		
	Periods *	−50 to +50	+50 to +100	100+	−50 to +50	+50 to +100	100+
Urine volume	1	4	1 (1) †	5 (1)	4	1	6
	2	6	3 (1)	1 (1)	5	3	3
	3	5	4	1 (2)	5	2	3
Urine sodium concentration	1	6 (2)	2	2	4	1	6
	2	4 (2)	2	4	3	1	7
	3	6 (2)	1	3	4	1	6
Urine potassium concentration	1	8 (1)	1 (1)	1	7	4	0
	2	8 (1)	1 (1)	1	8	1	2
	3	8 (2)	1	1	10	1	0
Urine chloride concentration	1	4 (2)	0	0	2	1	0
	2	2 (2)	1	1	2	1	0
	3	1 (2)	1	2	2	1	0

* Period 1, 6 a. m. to 2 p. m.; Period 2, 2 p. m. to 10 p. m.; Period 3, 10 p. m. to 6 a. m.
† Figures in parentheses indicate patients without heart disease.

The serum sodium and potassium levels were essentially unchanged. Within normal limits the serum sodium fell, especially from levels of 140 to 147 mEq. per liter, and rose, especially from levels of 128 to 137 mEq. per liter; similarly, serum potassium generally fell, after several days or weeks (never below 3.5 mEq. per liter), and occasionally rose from the lower levels (3.5 to 4.3 mEq. per liter). The hematocrit level did not change for several hours after administration (oral or intravenous) of the drug.

Single and Multiple Doses.—In Table 3 are listed the comparative effects of 500 mg. of acetazoleamide administered by mouth in a single dose or of four such doses over 24 hours. In patients with heart failure diuresis was only slightly more effective in the second and third eight-hour periods after multiple doses (see 100% + columns). The natriuretic effect of multiple doses was also more effective in many cases during the entire 24 hours of the multiple dose regimen and the day after (Table 4). There were no apparent differences in the less marked increases in urinary potassium and chloride concentrations with the two regimens.

Renal Clearances.—Table 5 lists the parallel effects on renal plasma flow (*p*-aminohippurate clearance), glomerular filtration rate

TABLE 4.—*Twenty-Four Hour Results of Oral Administration of Acetazoleamide, 500 Mg. Once (Eleven Cases) or Four Times (Twelve Cases) in Twenty-Four Hours, in Cases of Congestive Failure and in Two Patients Without Heart Failure*

		% Change After One 500 Mg. Dose Acetazoleamide, No. of Patients			% Change After Four 500 Mg. Doses Acetazoleamide, No. of Cases		
	Days	−50 to +50	+50 to +100	100+	−50 to +50	+50 to +100	100+
Urine volume	1st	7	2 (2) *	2	4	3	5
	2nd	7 (2)	2	2	6	2	4
Urine sodium concentration	1st	5 (2)	2	4	3	4	5
	2nd	3 (2)	2	6	5	8	4
Urine potassium concentration	1st	8 (2)	3	0	10	2	0
	2nd	8 (2)	2	1	10	2	0
Urine chloride concentration †	1st	2 (2)	1	1	2	1	0
	2nd	1 (2)	1	2	3	0	0

* Figures in parentheses indicate patients without heart disease.
† Chloride determinations done on four (500 mg. single dose) and three (500 mg. multiple doses) cases only.

TABLE 5.—*Per Cent Changes from Control Values for Forty-Five Minutes After 250 Mg. Acetazoleamide Intravenously*

Case	Diagnosis	RPF,* % Change	GFR,* % Change	Urine Vol., % Change	Urine Na, % Change	Urine K, % Change	Urine Chloride, % Change
No heart disease							
1	Peripheral neuritis	− 4	− 2	....	.....	.....	.....
2	Postpoliomyelitis	−16	− 6	....	+185	+283	+ 36
3	Chronic lung abscess	+13	−10	+ 9	+ 56	+133	+ 10
4	Hodgkin's disease	−12	− 1	+27	+370	+292	− 10
5	Bronchiectasis	− 3	−11	+18	+ 60	+339	− 13
	Average	− 4	− 6	+18	+170	+262	+ 6
Cardiac failure							
6	Hypertensive heart failure, Class III	−18	− 8	+65	+109	+ 44	+ 11
7	Arteriosclerotic heart failure, Class II	−13	−12	....	+ 40	+ 31	− 27
8	Arteriosclerotic heart failure, Class IV; old myocardial infarcts	− 1	+ 4	+117	+3,300	+392	+148
9	Arteriosclerotic heart failure, Class IV; old myocardial infarcts	− 7	+ 3	+51	+125	+152	− 18
10	Arteriosclerotic heart failure, Class IV	−19	+ 8	+16	+ 24	+ 41	− 16
11	Arteriosclerotic heart failure, Class III	+ 3	− 9	+57	+105	+100	+ 33
	Average	− 9	− 3	+61	+617	+127	+ 22

* RPF, renal plasma flow; GFR, glomerular filtration rate.

(mannitol clearance × 1.1), urinary volumes, and sodium, potassium, and chloride excretions summated for 45 minutes following administration of 250 mg. of acetazoleamide intravenously in five patients without cardiac disease and in six cases of cardiac failure. The renal clearances showed inconsequential falls; the chloride excretion generally rose (or fell) slightly. The urinary volume and sodium excretion rose, as expected, more markedly in cardiac than in normal subjects, obviously in no relation to any changes in the renal hemodynamics. Increased potassium excretion was apparently more marked in noncardiac than in cardiac subjects.

Ballistocardiographic Effects.—The Nickerson [6] formula was used: "Stroke volume" (probably measuring the systolic aortic blood impulse) in milliliters $= \frac{5.02 \times F \times P}{T \times L}$ (5.02 = a constant [for 35 gm. standardization]; F = I-J height in centimeters; P = $\sqrt{\text{mean SP} - \text{DP}}$; T = I-J interval in seconds; L = height of subject in centimeters). The "stroke volume" was generally found to be proportional to the I-J vertical distance, since the other factors remained almost constant. Likewise, the relative "cardiac outputs" ("stroke volumes" × heart rates) were also so proportional, since the heart rates were practically unaffected. In common with other workers we feel that the absolute cardiac outputs obtained by this method are not reliable. The relative changes are probably more so.

The changes from the controls for from 1 to 60 minutes following acetazoleamide 250 mg. intravenously are seen in Table 6. The "stroke volumes" were apparently unaffected in subjects without cardiac disease (Cases 1 to 4), variably affected (slightly depressed?) in cardiac patients not in heart failure (Cases 5 to 8), and generally raised in frank congestive failure.

As mentioned above, the arterial pressures and heart rates were affected little, the former, in general, reflecting slightly the rise or fall in "stroke volume." The venous pressures were generally unchanged or fell or rose in the same direction as the "stroke volume," at most 7% in 10 of the 18 cases.

Two patients (Table 6) deserve special consideration.

Case 6.—W. C., a 33-year-old white man, No. 3435K, was admitted to John Sealy Hospital Feb. 16, 1954, with a history of sharp and constricting anterior chest pain radiating to the left arm, aggravated by coughing. There were physical findings of harsh apical and aortic systolic murmurs, slight cardiomegaly, and hepatomegaly. ECG was compatible with subacute pericarditis. Sedimentation rate was 30 mm. in one hour (corrected). The patient was given cortisone for one week, then salicylates.

After administration of acetazoleamide, 250 mg. intravenously, the changes shown in Table 7 were noted.

Especially noteworthy is the rise in venous pressure and urinary excretion despite the fall in "cardiac output."

Case 7 (and 8).—J. S., a 23-year-old white man, No. 11118D, was admitted to John Sealy Hospital on March 26, 1954, with a history of recurrent rheumatic fever at ages 9 to 12 and progressive dyspnea on exertion since November, 1951, with recurrent "pneumonias" and hemoptyses. There were physical findings of cardiomegaly, mitral stenosis, and insufficiency; there was no frank congestive failure or rheumatic activity.

After acetazoleamide, 250 mg. intravenously, on two different occasions, the changes shown in Table 8 were noted.

Noteworthy is the fall in venous pressure in both instances, despite the fall in cardiac output before commissurotomy, which was not present postoperatively. Immediate diuresis and electrolyte excretion was marked in this case (preoperatively) after acetazoleamide, 250 mg. intravenously.

Enzyme Effects.—The following tables indicate that acetazoleamide has no significant in vivo effects on the activity of succinic dehydrogenase in the rat heart and kidney.

Succinic dehydrogenase activity (micrograms of tetrazolium dye reduced by 25 mg. homogenate in 30 minutes) one hour after acetazoleamide, 500 mg. (0.8 M) injected intraperitoneally, is shown here.

	Rat Heart	Rat Kidney
Control	54.0 ± 1.3 (S. D.)	59.4 ± 3.0
Acetazoleamide	62.2 ± 2.8	52.4 ± 3.0

TABLE 6.—*Per Cent Changes from Control Values of "Cardiac Output" (Aortic Blood Propulsion), as Indicated by Ballistocardiogram, After 250 Mg. Acetazoleamide Intravenously*

Case	Patient	Diagnosis	Minutes After Acetazoleamide						
			1	5	10	15	30	45	60
1	N. D.	Postpneumonia	− 8	−16	−12	− 1	− 8	− 9	− 8
2	R. P.	Hydradenitis	− 2	+ 4	+ 1	+20	− 1	+18	+28
3	J. G.	Healing duodenal ulcer	−11	−11	−10	0	− 8	0	0
4	A. R.	Essential hypertension; slight cardiomegaly, Class I	− 9	0	0	+14	+47	+59	+36
5	D. P.	Rheumatic mitral insufficiency; arrested subacute bacterial endocarditis, Class I	−10	−21	− 5	− 2	−12	− 1	+ 4
6	W. C.	Rheumatic mitral insufficiency; aortic stenosis and insufficiency; active (subacute) pericarditis, Class I	− 1	−19	−32	−31	−36	−32	−45
7	J. S.	Rheumatic mitral stenosis and insufficiency; enlarged heart, Class II	−23	−40	−55	−66	−43	−28	−33
8	J. S.	Case 7, 18 days after commissurotomy	+ 4	+ 4	+ 8	+12	+ 8	+16	+10
9	F. A. B.	Decompensated cirrhosis of liver; anasarca; enlarged heart; venous hypertension, Class IV	−36	−48	−36	−30	−30	−12	+ 9
10	R. A.	Hypertensive heart failure, Class III	+ 3	+40	+38	+66	−34	−23	−28
11	A. H.	Arteriosclerotic heart failure, Class III	+100	+300	+234	+167	+167	+167	+167
12	L. F.	Arteriosclerotic heart failure, Class IV	.....	+229	+179	+389	+235	+177	+148

TABLE 7.—*Results of Administration of Acetazoleamide, 250 Mg. Intravenously, in Case 6*

Minutes After Administration of Acetazoleamide	"Cardiac Output," %	Arterial Pressure	Pulse Rate	Venous Pressure	Urine Findings			
					Volume, %	Sodium, %	Potassium, %	Chloride, %
Control	0	126/82	92	19.3	....	.....	.....	.....
1	− 1	124/80	92	19.6				
5	−19	118/78	88	19.7	+ 6	+150	+188	+128
10	−32	122/76	92	20.1				
15	−31	120/78	92	20.8	+14	+ 73	+356	+ 24
30	−36	124/100	92	23.8				
45	−32	120/80	88	21.1	+18	+171	+300	+ 52
60	−45	118/78	92	22.5	....	.....	.....	.....

TABLE 8.—*Results of Administration of Acetazoleamide, 250 Mg. Intravenously, in Case 7*

Minutes After Administration of Acetazoleamide	"Cardiac Output," %		Arterial Pressure		Pulse Rate		Venous Pressure	
	B *	A *	B	A	B	A	B	A
0	0	0	116/78	108/64	112	112	17.8	26.3
1	−10	+ 4	114/72	100/60	116	108	17.6	....
5	−20	+ 4	110/68	100/64	112	116	16.9	....
10	−29	+ 8	110/60	100/64	112	112	14.7	25.6
15	−51	+12	110/70	100/66	108	108	14.2	....
30	−23	+ 8	162/66	100/64	108	112	13.4	24.9
45	− 3	+16	108/60	102/66	108	104	13.6	....
60	−33	+10	110/68	108/66	112	104	13.7	25.4

* B, 12 days before commissurotomy; A, 18 days after commissurotomy.

Smaller concentrations of acetazoleamide gave similar results.

Succinic dehydrogenase activity (micrograms of tetrazolium dye reduced by 25 mg. homogenate in 30 minutes) in vitro (16 determinations each) is shown here.

	Control	Acetazoleamide			
		0.0008 M	0.008 M	0.04 M	0.08 M
Heart	58.3	61.0	86.9	130.8	74.9
Kidney	58.4	62.4	97.1	81.9	25.0

The apparent increase in succinic dehydrogenase activity in vitro is not borne out by in vivo experiments (see above) nor by histochemical studies, which showed only occasional denser formazan deposition than the controls. Only huge doses (0.08 M +, above) cause diminution of activity in the kidneys in vitro.

Adenosine triphosphatase activity in the rat heart and kidney is likewise unaffected by acetazoleamide, as is shown in the following comparison with $HgCl_2$ and mercurophylline depression in vitro (16 determinations each; adenosine triphosphatase activity in micrograms of phosphorus liberated per milligram of homogenate per hour).

	Control	$HgCl_2$		Mercurophylline, 0.0013 M	Acetazoleamide, 0.065 M
		0.0013 M	0.0065 M		
Heart	27.9	13.6	6.4	18.2	27.5
Kidney	35.9	25.1	....	30.2	34.0

Similarly, higher concentrations of acetazoleamide (0.29 M) in another series of 14 experiments produced an insignificant depression of rat heart adenosine triphosphatase activity (19.9 ± 0.3 *vs.* 22.2 ± 1.1 for the controls).

COMMENT

Our results essentially confirm the previous reports † of significant diuresis following either single or multiple doses of acetazoleamide. Whereas in normal beagles,[7] however, the inhibition of carbonic anhydrase activity makes the renal tubules refractory to repeated doses after 6 to 12 hours, until the enzyme is reconstituted, in patients with heart failure continued diuresis usually occurs for 48 hours and often much longer. Nevertheless, since the water and electrolyte excretions are not too different in the case of single or multiple dosage, no great further inhibition of carbonic anhydrase is probably involved after the first dose has acted. Continued extracellular (and intracellular) fluid and electrolyte shifts perhaps occur in some way yet unknown, along with greater cardiac competency.

It is also evident that even multiple large doses do not cause severe serum electrolyte alterations. Even after prolonged acetazoleamide administration serum potassium did not fall below 3.5 mEq. per liter, nor were electrocardiographic changes seen. Similarly, even in combination with the low-potassium diet, acetazoleamide failed to reduce hypertensive blood pressures except in a few cases, as contrasted with the marked hypotensive effects of ammonium resin (Win 3000) plus potassium depletion.[10]

In cases of cor pulmonale respiratory acidosis was not clinically aggravated, since it is usually compensated, and the acetazoleamide merely serves by excretion of base to reduce the high CO_2-combining power to normal (in one instance from 93 to 63 vol. %, when the respirator had failed to do so [see above]). The alveolar and arterial pCO_2 actually falls [11] after acetazoleamide in cases of cor pulmonale. Still, it seems likely that the acetazoleamide inhibition of carbonic anhydrase is much more effective in the renal tubules than in the red blood cells (in relation to CO_2 transport) and elsewhere.

In attempting to rule out general and renal hemodynamic alterations as instrumental in acetazoleamide diuresis, as has been done for mercurials and xanthines, it is fairly evident that there are no immediate changes in blood volume (e. g., hematocrit level). The pulse rate, venous pressure, and arterial pressure remain constant. The cardiac output (ballistocardiographic) may rise or fall (these effects should be checked by the method of cardiac catheterization). The renal plasma flow

† References 7-9.

(*p*-aminohippuric acid clearance) and the glomerular filtration rate (mannitol clearance) are unchanged. Thus, even in the face of an occasional increase in cardiac output, glomerular filtration does not rise, even acutely (as in the case of aminophylline), and so tubular secretion and reabsorption factors are paramount in acetazoleamide diuresis. Similar findings have been recorded following intravenous (2 gm.) sodium *p*-sulfamyl benzoate (Dirnate),[12] a carbonic anhydrase inhibitor of lesser effect.

Carbonic anhydrase inhibition by acetazoleamide accounts for suppression of the reaction $CO_2+H_2O=H_2CO_3$ and the consequent H^+ (and HCO_3^-) release for excretion by the distal renal tubules.[7] Na^+ reabsorption from within the tubules is depressed because fewer H^+ ions are available for exchange with it across the tubular membrane.

K^+ ions, normally competing with H^+ ions for distal (?) tubular excretion,[13] are also consequently excreted in excess amounts; they are also probably reabsorbed less than normally. HCO_3^- ions are excreted, with diminished reabsorption, combined with the excess tubular Na^+ and K^+ ions. An "osmotic" water diuresis ensues. Potassium salts are diuretic in similar fashion: by hyperkalemic competition with H^+ ions for tubular reabsorption an alkaline urine with excess K^+, Na^+, and HCO_3^- results in the face of plasma acidosis.[14]

Both titratable acid (as urinary buffers, e. g., NaH_2PO_4) and ammonia (excreted as NH_4^+) concentrations in the urine present immediate falls.[7] As renal tubular glutaminase rises [15] follow administration of acetazoleamide, the availability of ammonia for excretion (normally preventing the loss of fixed bases, Na^+ and K^+) is forwarded. All agree that this occurs at least on the rebound from carbonic anhydrase depression. In the alligator, the ammonia excretion is unchanged following acetazoleamide, while the CO_2 excretion decreases [16] (instead of increases, as in other species). Hence, the supposed linkage between hydrogen and ammonium ion excretions does not hold, at least for that animal.

Theoretically, as is indicated in dog experiments,[7] chloride excretion should be unchanged or decreased (by exchange for bicarbonate excretion). In congestive heart failure, however, not only is cation and water excretion increased for days following a single dose (250 mg. or 500 mg.) of acetazoleamide—much beyond the expected interval of carbonic anhydrase inhibition and the maintenance of an alkaline urine—but the chloride excretion frequently rises markedly as well. Attempts to base this usual, though not invariable, chloruresis upon depression of oxidative enzyme activity, such as occurs with mercurial diuresis, have been unsuccessful (see above). It has been suggested that the usual alkaline cation tide may be followed by reverse effects (as are seen in dog experiments after 6 to 12 hours), with excessive subsequent excretion of ammonium chloride. However, following intravenous acetazoleamide (250 mg., see above), chloride excretion, like that of cations and water, usually rises immediately and continuously.

A variable amount of Cl^- must be carried along with the excess of unabsorbed Na^+ and K^+ ions within the renal tubules. Still, since the chloruresis is neither primary nor marked, no hypochloremia results; yet a refractoriness to further diuresis often occurs within several days of the start of acetazoleamide therapy. In some cases hyperchloremic acidosis is apparently responsible,[17] with the sparse loss of extracellular HCO_3^- being the limiting factor of diuresis. The administration of chloride, e. g. NH_4Cl, with acetazoleamide, in contrast to the synergistic effect of the former with mercurials, would, of course, only aggravate the high extracellular Cl^-: HCO_3^- ratio and result, as occurs clinically, in weight gain instead of weight loss. Similarly, in nephrosis or cirrhosis with anasarca acetazoleamide often fails as a diuretic, although hyperchloremia or acidosis are probably not the essential factors, being often absent.

Frequent chloride hyperexcretion is apparently not associated with any significant inhibition of succinic dehydrogenase or ad-

enosine triphosphatase activity by acetazoleamide in therapeutic doses, as it is in the case of mercurials. On the other hand, this very failure to inhibit oxidative enzymes is a functional corollary of the lack of toxicity of acetazoleamide with respect to the heart and kidney, organs which are among those severely injured by mercurials.

SUMMARY AND CONCLUSIONS

Acetazoleamide diuresis is associated with carbonic anhydrase inhibition in the renal tubules, producing an alkaline urine, excessive distal tubular excretion of potassium, and decreased tubular reabsorption of sodium and other cations, bicarbonate, and, consequently, water.

Lack of toxicity in the heart and kidney is evidenced by failure to inhibit the activity of succinic dehydrogenase and adenosine triphosphatase in those organs.

Such hemodynamic alterations as may occur after acetazoleamide administration do not contribute to its diuretic effect.

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ADULT AGAMMAGLOBULINEMIA

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AGAMMAGLOBULINEMIA was first described by Bruton [1] in a male child as a syndrome of recurrent bacterial infection associated with a lack of gamma globulin despite an otherwise relatively normal plasma protein pattern. Similar cases subsequently from other clinics also have been in male children.* In 1948, one of us (S. S.) prepared two pneumococcal vaccines for Colonel Bruton's patient, each of which failed to induce antibody formation. Subsequently Bruton demonstrated that this child's plasma proteins were deficient in gamma globulin. The failure of such children to develop immunity to infections would suggest that relatively few, prior to the antibiotic era, would have survived to adulthood. The purpose of this report is to describe this syndrome in two adults, one with repeated bacterial pneumonias and one with repeated infections associated with a sprue-like picture.

REPORT OF CASES

CASE 1.[6]—G. W. S., a 26-year-old white male farmer's helper, was admitted to the infectious disease service of the Ohio State University Hospital on Dec. 4, 1953, with the chief complaint of pain in his right chest of five days' duration. At this time he developed a severe cough productive of yellowish sputum, associated with right lower costal pleuritic pain. These symptoms increased in severity for the next two days, at which time his local physician was consulted and he was treated for "gall bladder" disease. The symptoms, however, progressed, and on the day of admission he began to vomit and had associated chills and fever. The past history is significant in that the patient had a cleft palate and a congenital hip dislocation repaired during childhood. He has been mentally retarded and has not been able to acquire the ability to talk. He has been able to perform simple chores on the farm, eat, and dress without assistance. In March and April, 1953, he was treated for pneumonia on two occasions at another hospital. The mother stated that he had not suffered recurrent infections until this year. She denied any double infection with any of the childhood diseases and remembered only that he had measles, mumps, and chicken-pox as a child. However, a review of our outpatient records revealed that this patient was treated in our clinic in January, 1950, and in April, 1953, for erysipelas of the face. The family history was not significant except for the fact that the father was supposed to be a "bleeder."

Physical examination revealed a well-developed well-nourished man in moderate respiratory distress. Temperature was 101 F.; pulse rate, 120; respirations, 40; blood pressure, 130/80. The pharynx was injected and swollen, and an incompletely closed cleft palate and double uvula were also noted. Examination of the chest revealed dullness to percussion over the right superior portion, posteriorly. Fine rales were heard, but tactile and vocal fremitus was greatly increased over this area. The abdomen was slightly tender and rigid in the right upper quadrant. The liver was felt 2 fingerbreadths below the right costal margin. There was marked deformity of both the patient's legs and feet. All other physical findings were within normal limits.

X-ray of the chest revealed a right upper lobe infiltrate with depression of the horizontal fissure. There was also evidence of some minimal fluid in the right base. The initial hemogram demonstrated a white blood cell count of 23,000, 82% of which were neutrophiles; the remainder of the hemogram and a bone marrow aspirate were within normal range. The urinalysis, blood serology, prothrombin time, bilirubin (van den Bergh), serum inorganic phosphorus, alkaline phosphatase, blood urea nitrogen, and serum electrolytes were all within normal range. The sputum, which was blood-tinged, revealed predominantly beta hemolytic streptococci and staphylococci on repeated examinations. On admission total serum proteins were 5.3 gm. per 100 cc., with 4.0 and 1.3 gm. of albumin and globulin, respectively. On Dec. 15, total proteins were 4.9 gm. per 100 cc., with 4.2 gm. albumin and 0.7 gm. of globulin. Repeated protein determinations during his hospital course lay within this range of values. On Dec. 8 thoracentesis from the seventh intercostal space in the posterior axillary line revealed 100 cc. of thin straw-colored fluid with a specific gravity of

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* References 2-5.

1.015; 3,025 red blood cells and 1,080 white cells per cubic millimeter, with 97% polymorphonuclear neutrophiles and 3% lymphocytes, and a total protein of 4,360 mg. per 100 cc. Cultures for both routine and acid-fast bacilli were negative.

After the institution of penicillin and streptomycin therapy the patient became afebrile on the third hospital day and remained essentially so throughout the remainder of his hospitalization. The right chest and abdominal pain remained for approximately one week and then disappeared concomitantly with the accumulation of the pleural fluid described above. The patient was discharged on the 16th hospital day considerably improved.

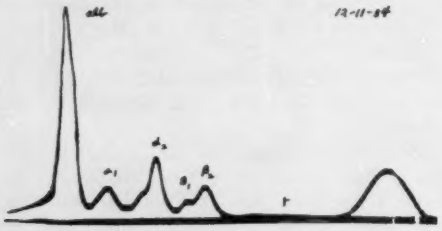

Fig. 1 (Case 1).—Tiselius boundary electrophoretic pattern of serum, showing absence of gamma globulin. Also shows elevation of alpha$_2$ globulin, as seen in lobar pneumonia. (Barbital buffer, pH 8.6, ionic strength 0.1, Aminco-Stern apparatus.)

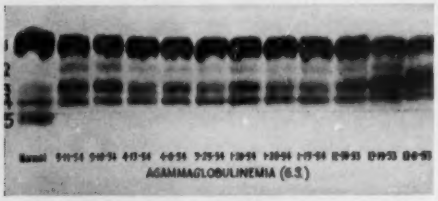

Fig. 2 (Case 1).—Durrum principle zone electrophoretic analysis (filter-paper) of 11 serial serum samples and normal control, showing lack of gamma globulin. Samples dated Dec. 8, Dec. 15, and Dec. 30, 1953, as well as samples dated May 10 and 11, 1954, show elevation of alpha$_2$ globulin, as seen in lobar pneumonia. Legend: 1, albumin; 2, alpha globulin; 3, alpha$_2$ globulin; 4, beta globulin, and 5, gamma globulin. (Barbital buffer, pH 8.6, ionic strength 0.05, Wall modification of Durrum apparatus.)

Special Studies.—With the history of multiple infections, repeated electrophoretic studies of this patient's plasma, during his hospital stay and subsequently, revealed an absence of gamma globulin (Figs. 1 and 2). Immunologic studies demonstrated that this patient did not form any antibodies in response to inoculations with triple typhoid, influenza, and mumps vaccines. Histoplasmin, tuberculin, and toxoplasmin skin tests were negative. The patient had a positive Schick test and negative heterophile, cold agglutinin, and antistreptolysin titers. The patient's blood type was A, Rh-positive (D), and his anti-B titer in saline solution was only 1:8. Electrophoretic patterns of both his parents' plasmas were within normal range.

Subsequent Admissions.—The patient was readmitted on March 24, 1954, at which time a diagnosis of coryza was made, and again on May 8, when he was admitted with left upper quadrant pain of two days' duration. At this time he had a temperature of 103.4 F., pulse rate of 90, and respirations, 35. Physical examination revealed dullness in the left base of his chest, with harsh breath sounds and rales. His white cell count on admission was 20,950, with 85% neutrophiles and 15% lymphocytes.

Cultures of his sputum consisted predominantly of hemolytic Staphylococcus aureus. Total serum proteins were 5.3 gm., with albumin 4.5 gm., and globulin 0.8 gm. X-ray of the chest revealed a bronchopneumonia on the left side. The patient responded promptly to penicillin therapy and was discharged on May 13.

Serologic studies at this time revealed that he had not yet formed antibodies following his previous immunizations and was negative to the mumps skin test antigen despite prior "immunization."

CASE 2.—J. F., a 40-year-old white male lawyer, was first seen in December, 1951, with fatigue, diarrhea, nasopharyngitis, and minimal lymphadenopathy. As the fatigue and upper respiratory symptoms persisted, an axillary lymph node biopsy was performed in January, 1952. This biopsy showed reticulum cell hyperplasia. His hemogram was normal. Cultures and guaiac tests of stools were negative. The total serum protein was 5.2 gm. per 100 cc., with 4.31 gm. of albumin and 0.89 gm. of globulin. Van den Bergh, thymol turbidity, blood urea nitrogen, fasting blood sugar, cephalin flocculation, alkaline phosphatase, Wassermann, and heterophile and cold agglutination tests were all normal. Sigmoidoscopy revealed a reddened hyperemic mucosa with some fine "pebbling." Bone marrow examination was within normal limits. A chest x-ray showed a slight increase in the bronchovascular markings An upper gastrointestinal series and barium enema were normal.

The lymph node biopsy site failed to heal for two and one-half months despite vigorous antibiotic therapy. In April, 1954, the patient had a recurrence of pharyngitis and diarrhea. The following month he developed a furuncle on his right thigh, which was extremely slow in healing. In July, 1952, there was another bout of severe diarrhea. Sigmoidoscopy in August, 1952, showed a granular mucosa which bled easily on trauma. Upper gastrointestinal and barium enema x-rays at this time showed slight hepatosplenomegaly and an irritated small bowel mucosal pattern suggestive of "a deficiency state or

diffuse enteric disease." He was given liver injections, methantheline (Banthine), a pancreatic enzyme, and a therapeutic vitamin preparation. His diarrhea subsided. In October, 1952, the patient had a protracted upper respiratory infection with bilateral purulent conjunctivitis, which was treated successfully with penicillin. In November, 1952, he developed severe diarrhea and was once again hospitalized.

The total serum protein was 5.6 gm. per 100 cc., with 4.8 gm. albumin and 0.8 gm. globulin. Hemogram, urinalysis, Wassermann test, thymol turbidity, cephalin flocculation, urinary 17-ketosteroids, and Thorn corticotropin test all were normal. Electrocardiogram was normal. Upper gastrointestinal and barium enema x-ray studies were essentially as described previously. In January, 1953, diarrhea recurred with an upper respiratory infection and both responded to penicillin and antispasmodics. There was another episode of diarrhea in June, 1953, followed by bronchitis with purulent sputum in August, 1953. In September, 1953, severe diarrhea recurred and the patient was hospitalized

Fig. 3 (Case 2).—Durrum principle zone electrophoretic analysis (filter-paper) of 11 serial serum samples and normal control, showing lack of gamma globulin. Legend: 1, albumin; 2, alpha globulin; 3, alpha$_2$ globulin; 4, beta globulin, and 5, gamma globulin. (Barbital buffer, pH 8.6, ionic strength 0.05, Wall modification of Durrum apparatus.)

at the Ohio State University Hospital. The diarrhea at this time was watery with some mucus and with a frequency of six to seven stools per day, but, as with all his previous diarrheas, there was no melena. There had been no weight loss. There was no lymphadenopathy, splenomegaly, or hepatomegaly. The hemogram and urinalysis were normal. Total serum protein was 5.2 gm. per 100 cc., with 4.2 gm. albumin and 1.0 gm. globulin. The sulfobromophthalein (Bromsulphalein) excretion test, blood urea nitrogen, van den Bergh test, thymol turbidity, cephalin flocculation, and serum cholesterol were normal. One of us (R. W.) saw this patient at this time and, struck by the low serum globulin and repeated infections, performed an electrophoresis of this patient's serum (Fig. 3). It was evident that this patient lacked gamma globulin. Serial electrophoretic analyses were made on this patient's serum in the subsequent 10 months, and representative patterns are shown in Figure 3. This patient was in blood group A and totally lacked anti-B isoagglutinins. In November, 1953, he developed a left basilar bronchopneumonia and in December, 1953, and again in February, 1954, experienced a maxillary sinusitis and bronchitis, with a recurrence of diarrhea in March, 1954. A course of immunization with typhoid-paratyphoid vaccine resulted in no antibody response to both O and H antigens.

COMMENT

Agammaglobulinemia is a syndrome which may be found in adults as well as in children. The repeated infections in the two patients described in this report could be attributed to their deficiency of gamma globulin and concomitant poor antibody response. By conventional boundary electrophoresis, the sera of both patients could be described as completely lacking gamma globulin. However, by zone (filter-paper) electrophoresis small quantities (1.0 to 1.5%) of the total protein could be estimated as representing gamma globulin. The remainder of the serum electrophoretic patterns of both men was entirely normal except for the expected elevation of the alpha$_2$ fraction with each episode of pneumonia in one of the patients.

Whether this syndrome in both patients represents a congenital or an acquired defect in gamma globulin synthesis is difficult to ascertain. It is tempting to suggest that the syndrome was congenital in the patient with the multiple congenital defects. His lack of repeated childhood infections could be explained by his isolated mode of living. On the other hand, the second patient had always lived in an urban community and without previous repeated childhood infections. His defect would apparently be most likely to have been acquired.

With the possibility that both patients had acquired the syndrome, one is still faced with the question of pathogenesis. Agammaglobulinemia can be associated with nephrosis and has also been seen in two cases of advanced lymphoma in this institution. Neither of the patients described in this report showed any evidence of renal or reticuloendothelial disease. With the increased application of filter-paper electrophoresis as a relatively simple procedure, more cases of agamma-

globulinemia should be recognized in both children and adults. In fact, during this study, agammaglobulinemia has been reported in adults by Young and Wolfson [7] and by Sanford and associates.[8]

SUMMARY

The syndrome of agammaglobulinemia was observed in two adults. One case was characterized by a sprue-like syndrome with multiple other infections over a three-year period of observation. The other case was characterized by repeated attacks of bacterial pneumonia.

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TREATMENT OF LOCALIZED HISTOPLASMOSIS WITH 2-HYDROXYSTILBAMIDINE

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THE TREATMENT of histoplasmosis, particularly of the progressive disseminated type, has been for the most part unsuccessful. In vitro studies by Seabury and Artis [1] revealed that stilbamidine is an effective histoplasmocidal agent, and Snapper has shown that 2-hydroxystilbamidine inhibits the growth of histoplasma capsulatum in vitro in concentrations of 20 to 40 γ per milliliter.[2] Because of these findings and inferred benefit from stilbamidine in disseminated cases, we felt that a clinical trial with 2-hydroxystilbamidine was indicated in a case of localized histoplasmosis of the hard palate recently admitted to the Veterans Administration Hospital, Hines, Ill.

REPORT OF A CASE

A 53-year-old white man, a cattle farmer from Nebraska, first noted a painful area involving the gingiva in the region of his left upper premolar teeth in May, 1953. A small nodule developed in this area, and approximately one month after onset of symptoms it became ulcerated. At this time the patient also noted a small area of tenderness and subsequent ulceration of the gingiva behind the lower incisor teeth. In July, 1953, he was treated for "trench mouth" by a dentist, without improvement. He consulted a second dentist, who advised hospitalization because of the possibility of malignant disease. Biopsy of the lesion at a hospital near his home in October, 1953, was interpreted as showing a squamous cell carcinoma. Radical surgery was then considered, including a resection of the left maxilla. Because the necessary dental laboratory facilities were not available for making the postsurgical prosthesis, the patient was referred to Hines Hospital, where he was admitted to the Tumor Service on Oct. 30, 1953. In the five-month period prior to admission he had lost 10 lb. (4.5 kg.), which he attributed to being unable to eat properly because of pain about the lesion. Otherwise he was asymptomatic.

Physical examination revealed a well-developed well-nourished white man who did not appear to be acutely or chronically ill. Positive findings were confined to the mouth. There was noted on the left midportion of the lower lip a 1 cm. raised grayish-white plaque with an indurated base. On the left hard palate was seen an ulcerated painful lesion measuring about 4 cm. in diameter, which extended from the last molar posteriorly to the premolar anteriorly and to the midline medially. The edges were raised, and the base was firm and gray and did not bleed following trauma (Fig. 1). A grayish-white tender granular area was present on the gingiva behind the left lower incisor teeth. There was no hepatomegaly, splenomegaly, or adenopathy.

X-rays of the chest, mandible, skull, and paranasal sinuses were reported as normal. Urinalysis, serologic studies, complete blood cell count, sedimentation rate, total protein, A/G ratio, thymol turbidity, alkaline phosphatase, and cephalin flocculation were all negative or within normal limits.

Punch biopsy specimens were taken from the lesion of the hard palate on Nov. 5, 1953. Microscopic examination revealed Histoplasma capsulatum organisms and inflammatory cells consisting of plasma cells, eosinophiles, lymphocytes, polymorphonuclear leucocytes, and atypical Langhan's giant cells (Fig. 2). A slide of the original biopsy, taken in Nebraska, was reviewed by the pathology department of this hospital and showed a histological picture similar to that described above. A biopsy of the lesion of the lower lip was interpreted as showing leucoplakia.

Skin test with histoplasma antigen 1:100 was positive. A sternal bone marrow specimen was interpreted as being normal. Culture of the marrow revealed no yeast or fungi. Culture of the oral lesion was positive for H. capsulatum.

Therapy with oxytetracycline (Terramycin), 250 mg. four times a day, was given from Nov. 7 to Nov. 17, 1953, without any change in the oral lesions. On Nov. 25, 1953, 2-hydroxystilbamidine therapy was instituted. One hundred fifty milligrams in 200 cc. of isotonic sodium chloride solution was given intravenously over a 30-minute period daily. A total of 20 gm. was given without any adverse effects except for some anorexia, nau-

From the Veterans Administration Hospital.

Fig. 1.—Ulcerated lesion on hard palate as it appeared on admission.

sea, and vomiting necessitating discontinuing the drug on one occasion, from March 18 to March 25, 1954. Prior to March 18 the patient had had no difficulty and had received 16.8 gm. of 2-hydroxystilbamidine. After restarting therapy he had no further symptoms. Several carious teeth were extracted. After 13.5 gm. of 2-hydroxystilbamidine had been given, the lesion behind the lower incisor teeth had completely healed and the lesion of the hard palate had almost completely granulated except for a small area adjacent to the first molar tooth (Fig. 3). After extraction of this tooth complete healing occurred. A biopsy of the lesion at the time of extraction revealed inflammatory cells with a great many plasma cells. No histoplasma organisms were identified.

An x-ray of the chest prior to discharge from the hospital was normal, and there was no clinical evidence of any dissemination of the disease.

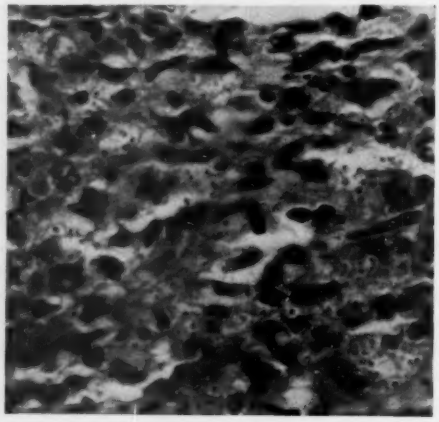
COMMENT

The numerous agents which have been used in the treatment of histoplasmosis is proof of the therapeutic dilemma which exists at the present time. Among these are bismuth compounds, potassium iodide, quinine, penicillin, stibamine glucoside (Neostam stibamine glucoside), stibophen, U.S.P. (Fuadin), sulfadiazine, cycloheximide (Acti-Dione), glucosulfone sodium (Promin), mercurials, streptomycin, chlortetracycline (Aureomycin), chloramphenicol, ethyl vanillate, and stilbamidine.

Most of these agents have given disappointing results. Ethyl vanillate has been used by a number of investigators, with varying results. Christie and co-workers treated 12 patients with culturally proved progressive disseminated histoplasmosis with this compound, 5 of whom were alive and well 1 to 15 months after therapy.[3] It was felt by the author that all would have died in a matter of a few weeks or months if left untreated. Ethyl vanillate orally and propamidine topically to a granulomatous lesion of the epiglottis was used by Ellis and co-workers in one case of disseminated disease, with evidently complete remission for nine months.[4] Locket and co-workers, on the other hand, reported one case treated without any obvious benefit.[5] The margin of safety of this drug is only about 25 to 30%, which is too small for a desirable therapeutic agent.

Improvement noticed in a patient treated with stibamine glucoside, an antimony preparation, whose disease initially was misdiagnosed as leishmaniasis, led to further investigation of this drug and a diamidine preparation, stilbamidine, by Parsons and Zarafonetis.[6] Two cases were treated, one showing "striking improvement," the second being unsuccessful. Seabury treated two cases with stilbamidine, which resulted in

Fig. 2.—Photomicrograph of the punch biopsy material taken from the lesion on the hard palate. Histoplasma capsulatum organisms are present.



temporary improvement but, according to the author, did not alter the course of the disease significantly.[7] The first patient received 7,457 mg., and the second, 6,275 mg. Whether these doses are adequate is a moot point; however, larger doses are not feasible because of toxic manifestations, particularly trigeminal neuralgia. It has been determined that the larger the total dose the more intense is the resulting neuralgia.

Because of this toxicity, a search for a more desirable drug led to the development 2-hydroxystilbamidine. It has been used in the treatment of multiple myeloma without

Fig. 3.—Appearance of lesion on hard palate after 13.5 gm. of 2-hydroxystilbamidine. The small area next to the molar healed after extraction.

the development of neuralgia or other toxic manifestations [8] and has been successful in producing remissions in blastomycosis.* Recently, large total dosage has been used in the treatment of disseminated coccidioidomycosis, without significant untoward symptoms.† In the treatment of our case the patient did develop transient anorexia, nausea, and vomiting after receiving 16.8 gm. of the drug. Medication was discontinued and restarted again in one week without any recurrence of the adverse symptoms. It is quite doubtful whether these symptoms were a manifestation of toxicity of the 2-hydroxystilbamidine. No pathologic neurological symptoms or signs were evident during the hospital course.

The complete healing of the oral lesions may be attributable to the therapy with 2-hydroxystilbamidine; however, it is well substantiated that localized lesions of histoplasmosis may be self-limiting and clear spontaneously without any treatment. Because of the excellent results in this case and the encouraging in vitro studies, we feel that further clinical use of 2-hydroxystilbamidine should be carried out in the progressive disseminated type of histoplasmosis.

SUMMARY

A report of one case of localized histoplasmosis treated with 2-hydroxystilbamidine is presented.

A total dose of 20 gm. of 2-hydroxystilbamidine was used without any evidence of toxic manifestations.

Complete healing of ulceration of the hard palate and gingiva due to histoplasmosis occurred. It appears that 2-hydroxystilbamidine is an effective agent in the treatment of Histoplasma capsulatum infection, and it is recommended that further evaluation of the efficacy of this drug be carried out.

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GASTROINTESTINAL BLEEDING IN HEREDITARY HEMORRHAGIC TELANGIECTASIA

Review of the Literature and Report of a Case with Severe Recurrent Hemorrhages Necessitating Total Gastrectomy

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HEREDITARY hemorrhagic telangiectasia (Rendu-Osler-Weber disease) is a hereditary vascular anomaly characterized pathologically by multiple dilatations of capillaries and venules of the skin and mucous membranes and characterized clinically by recurrent hemorrhage from these telangiectasia, most frequently manifested by epistaxis. The entity is often overlooked or the bleeding attributed to some other cause, especially a blood dyscrasia. In gastrointestinal bleeding, peptic ulcer is often suspected, and, indeed, the two conditions may be present concurrently.

The condition was probably first reported by Sutton,[1] in 1864, as internal hemorrhage and telangiectasia of the skin. The following year Babington [2] described a family showing a tendency to epistaxis but made no mention of the presence of telangiectasia of the skin or mucous membrane in any members of the family. Rendu,[3] in 1896, reported a case of a 52-year-old man who suffered from repeated epistaxis and who had small superficial angiomata of the skin of the face, neck, thorax, and mucous membranes of the mouth. This patient's mother and one brother also had repeated epistaxis. The patient's father had been subject to melena. However, this condition was not recognized as a clinical entity until Osler's [4] work in 1901, when he described all of its curious manifestations with the exception of pulmonary angiomatosis or pulmonary arteriovenous aneurysm, which was apparently not recognized in any cases prior to the mid-1940's. Weber,[5] in 1907, and Hanes,[6] in 1909, made further contributions in clarifying the clinical and pathological characteristics of the disease. It was Hanes who suggested the descriptive terminology of hereditary hemorrhagic telangiectasia, which indicates the diagnostic triad of (1) familial history, (2) repeated hemorrhage, (3) multiple telangiectasia. Since then, as indicated by the extensive literature reviews of Goldstein * and Barrock,[9] numerous case reports and discussions of this disease have been presented, mostly by dermatologists and otolaryngologists, because of the skin lesions and the most frequent source of bleeding, the nasal mucous membrane.

The disease, as the name implies, is hereditary, being transmitted as a simple dominant factor, not sex-linked, and therefore affecting both sexes. No cases were reported in the Negro race until 1948, but since then three reports,† involving 11 persons, have been published. There are some patients with characteristic telangiectasia and hemorrhage who do not have a familial history. Fitz-Hugh [13] explains this on the basis of atavism.

The telangiectasia are most frequently found about the face, especially on the nasal and oral mucous membranes, but may occur in any organ of the body.[14] They often do not become apparent until the second decade and may not appear until much later in life. The lesions may be pin-point in size or larger, ranging up to papular areas several millimeters in diameter. Less frequently the lesions may be spider-like. The lesions are

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* References 7 and 8.

† References 10-12.

generally bright red, violaceous, or purple and partially blanch on pressure. Histologically, the vascular wall is extremely thin, often consisting of only a single layer of endothelium, lying immediately below the markedly thinned out epidermis.[15] The most frequent symptom is repeated epistaxis, which may precede any visible signs of telangiectasia. However, hemorrhage may occur from any area where telangiectasia are present. The hemorrhages generally become more severe and more frequent as the patient's age advances [14] and seem to be aggravated by anemia,[15] setting up a vicious cycle. The only characteristic finding, other than the appearance of the telangiectasia, is the secondary anemia which results from hemorrhage. Splenomegaly has been reported,[16] and this finding in the disease has been recently reviewed by Baker.[17] Characteristically, there is no evidence of blood dyscrasia and the capillary resistance is normal. However, Singer and Wolfson [18] reported three cases of hereditary hemorrhagic telangiectasia with a positive Rumpel-Leede tourniquet test, and Wells [19] reported two cases with a positive tourniquet test, two with prolonged bleeding time, two with variable clot retraction, one with variable coagulation time, and one with decreased platlets.

The complications of the disease are those associated with repeated and often severe hemorrhage with resulting anemia. The prognosis must be guarded because of the fact that hemorrhage may occur at any time. A mortality of 4% from the disease itself has been reported.[14] Treatment is directed toward control and prevention of hemorrhage and is in general unsatisfactory. The use of calcium, snake venom, sclerosing solutions, radium, x-ray, and electrocautery have been reported as being effective in some cases. More recently rutin has been used with varying results. One patient,[20] treated with topical thrombin, made a good response. Koch, Escher, and Lewis [21] have recently treated five cases with estrogen or combined estrogen-androgen therapy, with decrease in the frequency and severity of epistaxis. Very recently adrenochrome complex has been reported as effective in stopping hemorrhage from this disease.[22] However, blood transfusions to replace severe blood loss and iron preparations to aid in combating the secondary anemia seem to be the only universally accepted therapy.

This disease is uncommon but is being diagnosed more frequently now that more physicians are aware of the entity. Garland and Anning [23] stated in 1950 that 244 families had been reported, and they added 20 more. In 218 of these families, where the case records are fairly complete, 1,451 persons were affected. At the Mayo Clinic, 31 cases were recognized in the years 1920-1944, inclusive.[24] As stated before, most of the reported cases have been of epistaxis, though bleeding from almost every organ has been reported, the diagnosis of involvement of these organs being based on circumstantial evidence in some cases and on pathologic proof in others. This paper is concerned with hereditary hemorrhagic telangiectasia with involvement of the gastrointestinal tract.

The father of the patient reported by Rendu [3] had recurrent melena, but the exact cause was undetermined. One of Osler's [4] cases with proved hereditary hemorrhagic telangiectasia involving the nasal mucous membranes and face also had carcinoma of the stomach and hematemesis. At autopsy, in addition to the carcinoma, several typical telangiectasia were found in the stomach. Since that time a number of cases of proved hereditary hemorrhagic telangiectasia have been reported with associated hematemesis or melena, leading to the impression that the patient also had bleeding telangiectasia of the gastrointestinal tract. In about one half of these cases, the diagnosis of gastrointestinal involvement has been made only by exclusion of other known cause for the bleeding and is therefore not proved. In the other half, the diagnosis has been proved by autopsy, laparotomy, sigmoidoscopy, or gastroscopy.

Osler [4] reported a case in which telangiectasia were found in the stomach at autopsy. Fox [25] reported two cases of probable hereditary hemorrhagic telangiectasia with rectal

bleeding, but there was no proof of gastrointestinal lesions. Harper [26] reported a case with melena but no proof of gastrointestinal lesions. Boston [27] reported three cases with hereditary hemorrhagic telangiectasia with hematemesis. In one case lesions considered to be telangiectasia were found at autopsy; in one case, at laparotomy, and in the third case there was no proof of gastrointestinal lesions. Fitz-Hugh [16] reported a case with rectal bleeding, in which the lesions were seen at sigmoidoscopy. Hurst and Plummer [28] reported one case without gastrointestinal symptoms or known bleeding but with telangiectasia seen at sigmoidoscopy; one case with nausea, vomiting, hematemesis, and blood in the stools, in which sigmoidoscopy showed no abnormalities; one case with indigestion and one with rectal bleeding, in both of which telangiectasia were revealed by sigmoidoscopy, and one case with hematemesis and rectal bleeding, in which endoscopic examination was not done. Meikle [29] reported a case of hereditary hemorrhagic telangiectasia with rectal bleeding but without proof of gastrointestinal lesions. Schuster [30] reported a patient who had had no gastrointestinal symptoms but who had telangiectasia in the stomach and duodenum at autopsy. This patient also had several aneurysms in the pulp of the spleen and in the splenic artery.

In 1939, Renshaw [31] did a gastroscopic examination on a patient who had hereditary hemorrhagic telangiectasia with asymptomatic melena and found 20 millet-seed to pinhead-sized bright red slightly raised lesions distributed over the gastric mucosa. Sigmoidoscopy showed no abnormality. This is the first reported case of telangiectasia demonstrated gastroscopically in this disease. In 1941, Griggs and Baker [32] reported three patients with melena, one of whom had a negative gastroscopic examination and two of whom were not examined endoscopically. Stellar [33] reported a case with unexplained melena, but proof of gastrointestinal telangiectasia was lacking. According to the hospital records, this patient's mother had epistaxis, anemia, and telangiectasia of the lips and the autopsy report recorded "severe anemia and multiple bleeding points in the gastric mucosa." In 1944, Wolfsohn [34] reported a case with gastroscopically proved lesions. Rundles [35] reported a case with tarry stools and gastrointestinal distress. Gastroscopic examination revealed clusters of red circumscribed telangiectasia on the lesser curvature and anterior wall of the stomach. Sigmoidoscopy showed no abnormality. In 1946, Gambill [24] reported a case with melena and hematemesis but without proof of gastrointestinal telangiectasia. The same year, Kushlan [36] reported a case with melena, in which gastroscopy revealed numerous mucosal telangiectasia, 1 to 10 mm. in diameter, some of which were oozing blood at the time of examination. Proctoscopy showed no abnormalities.

Goldstein [8] reported two cases of hereditary hemorrhagic telangiectasia with hematemesis but without proof of gastrointestinal lesions. Bell [37] reported a case with repeated gastrointestinal bleeding, which at laparotomy revealed numerous dilated varicose veins on the serosa of the small bowel. The patient's aunt had had surgery for gastrointestinal bleeding and was found to have diffuse cavernous hemangioma of the jejunum. The patient's father also had gastrointestinal bleeding. This patient had not had epistaxis or visible telangiectasia on the skin, but the author considered him to be a case of hereditary hemorrhagic telangiectasia. Plummer, Burke, and Williams [20] reported a case with melena. Sigmoidoscopy and gastroscopy revealed no lesions, but at laparotomy many stellate telangiectasia were seen on the serosa from the proximal jejunum to the terminal ileum. Rumball [38] presented a case with rectal bleeding in which sigmoidoscopic examination revealed one telangiectasia and gastroscopic examination revealed several areas of cherry red telangiectasia on the greater curvature of the stomach. Goldman, Asher, and Ware,[39] in 1949, reported two cases in which gastroscopy revealed typical telangiectasia. Brandel [40] reported a patient with hematemesis but without proof of gastrointestinal telangiectasia. In 1950,

Kleinschmidt and Schwartz [21] reported a case in which epistaxis was generally accompanied by bright red rectal bleeding, but proof of rectal lesions is lacking. In 1953, Doenges [41] reported a patient with epistaxis and hematuria who also had tarry stools and hepatosplenomegaly, but there was no endoscopic proof of gastrointestinal lesions.

Several of the afflicted members of the extremely large Mormon family studied by Dolowitz [42] died of gastrointestinal hemorrhage, but there was no proof of gastrointestinal telangiectasia, because autopsies were not done.

In 1953, Baker [17] reported a family of 32 persons in four generations in which 12 members had evidence of hereditary hemorrhagic telangiectasia. Five of these members had frank hematemesis with melena, or melena alone, and two of these five also had hepatosplenomegaly later in the course of their disease. In only one of the five was there gastroscopic proof of telangiectasia.

In 1953, Shepherd [43] reported a case of hereditary hemorrhagic telangiectasia with coexisting carcinoma of the stomach, and at laparotomy numerous telangiectasia were found on the serosa of the proximal 4 ft. (120 cm.) of jejunum. His second patient had hematemesis, but gastroscopy, sigmoidoscopy, and laparotomy failed to reveal any telangiectasia of the gastrointestinal tract. The author's third case was that of a 54-year-old man with hereditary hemorrhagic telangiectasia who had a partial gastrectomy in 1950 because of indigestion and hematemesis. A large duodenal ulcer was found. A year later, gastrointestinal bleeding recurred and further laparotomy was performed, revealing a vigorous bleeding point on the posterior wall of the stomach. A cuff of tissue including the bleeding point was resected. Two weeks later bleeding recurred and a few "nevoid" patches were seen gastroscopically. On again opening the stomach at laparotomy, several angiomatous areas were observed to be bleeding. These were cauterized, but the patient died shortly after operation. The gastric mucosa taken at operation revealed no histologic abnormality. One minute ulceration was found at autopsy. In contrast to nearly all of the above reported patients, this patient had never had nose bleeds. He did have typical telangiectasia on the tongue and lips, as did also his sister. This last case has been presented in more detail because of its similarity to the following case report.

REPORT OF CASE

A 51-year-old white man was admitted to the Veterans Administration Hospital, Washington, D. C., for the first time in January, 1954, because of hematemesis. He had begun having intermittent epigastric distress three years previously and, shortly thereafter, was hospitalized elsewhere because of hematemesis and melena. He received three 500 cc. blood transfusions, and, after a gastrointestinal series, he was told that he had an "ulcer

Fig. 1.—Telangiectasia on lips and tongue.

of the stomach." After a repeat study, several months later, the patient was told that he no longer had an ulcer. For the following two years the patient experienced occasional epigastric distress and occasionally noticed dark stools, but he remained essentially well. One year prior to the present hospital admission the patient developed hematemesis and melena which required admission to another hospital, where he received five blood transfusions. An upper gastrointestinal series then, and another eight months later, revealed findings which were interpreted as hypertrophic gastritis, but no ulcer was demonstrated. During the following 11 months, the patient had three more hospitalizations and 12 more 500 cc. blood transfusions because of recurrent hematemesis and melena. A subtotal gastrectomy was performed in December, 1953, the patient receiving 2,000 cc. of blood during this period. The surgery and early postoperative period were uneventful, but 22 days after operation the patient had another hematemesis and required three more 500 cc. blood transfusions. He had been discharged from

that hospital only the day before the hematemesis which necessitated admission to this hospital.

Past history revealed pneumonia with empyema 30 years prior to admission, with a chronic cough and intermittent wheezing since. He had known for many years that he had an enlarged heart and had frequent episodes of rapid heart action. The patient did not bruise easily nor bleed excessively from trauma.

Physical examination revealed marked pallor and moderate weakness and dyspnea. The blood pressure was 120/60; pulse rate, 96; respirations, 32. The skin was pale, sweaty, and cool. On the lower lip there were 20 purplish-red areas, varying from pin-point size to 2 mm. in diameter (Fig. 1). The larger ones were slightly elevated and partially blanched on firm pressure. On the margin and undersurface of the tongue and on the floor of the mouth were distributed about 20 more of these lesions. At the posterior margin of the right nares were two dilated vessels, resembling spider angiomata. None were seen on the nasal mucous membrane. A complete nasopharyngeal examination was not done. A similar lesion was seen on the left aspect of the neck. There were two 1 mm. in diameter punctate red areas in the right palpebral conjunctiva. Over the anterior chest were 20 ruby-red nonblanching papular nevi, which did not resemble the lesions on the lips and face. On questioning, the patient stated that he had had these lesions almost all his life and that several other members of his family also had similar areas on their lips (see below for family history). There was slight palmar erythema. The lungs revealed bibasilar medium moist inspiratory rales and a few scattered rhonchi. The heart was moderately enlarged and revealed frequent extrasystoles and a Grade III systolic and diastolic aortic murmur. The abdomen revealed a healing right upper quadrant surgical scar, mild tenderness around the scar and in the epigastrium, and hyperperistalsis. There was no hepatomegaly or splenomegaly. Rectal examination revealed dark purplish-brown feces, which were strongly positive for occult blood.

Laboratory studies on the evening of admission showed that the hematocrit value was 26 vol. %; the white blood cell count and differential count, normal, except for 7% eosinophiles. The prothrombin time was 70%; bleeding time, 2 minutes; coagulation time, 6 minutes 55 seconds, and clot retraction, complete in less than two hours, forming a firm clot. The blood type was A-positive. Subsequent laboratory examinations revealed the prothrombin times and bleeding times to be within normal limits. The coagulation time (Lee-White) varied from 4 to 20 minutes in different laboratories, the clot retraction was always normal, and blood platlets varied from 158,000 to 503,000. Prothrombin consumption and plasma recalcification time were normal. Reticulocyte count, blood indices, and red cell fragility were normal. Rumpel-Leede tourniquet test was strongly positive (30 to 50

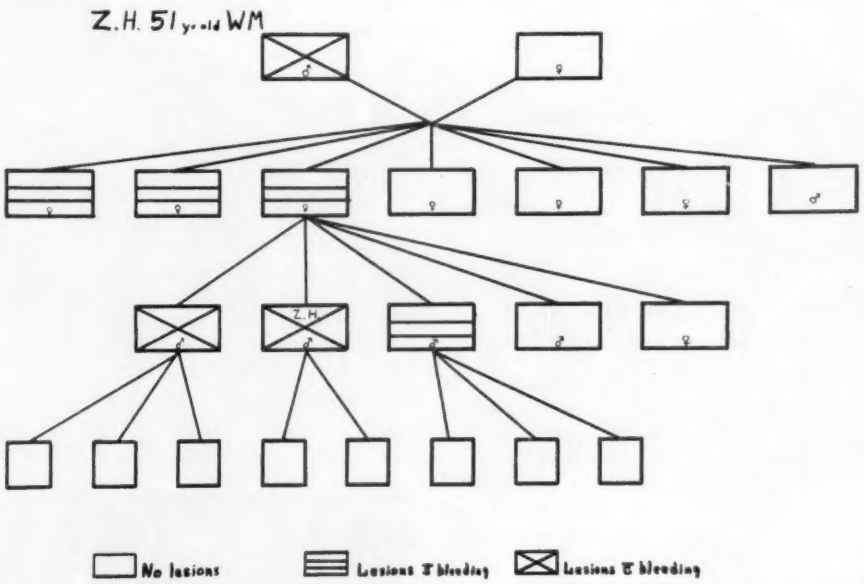


Fig. 2.—Chart representing family tree of the patient, Z. H., indicating the members manifesting telangiectasia and hemorrhage.

Fig. 3.—Patient's brother; telangiectasia on lips.

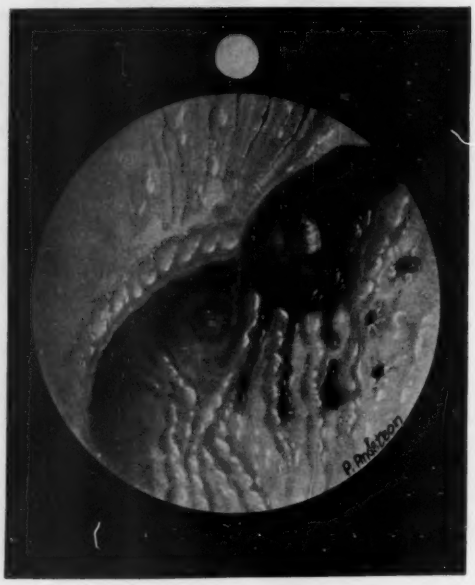
petechiae in 2.5 cm. circle) on four determinations. The sulfobromophthalein (Bromsulfalein) test revealed 8% retention in 45 minutes. Thymol turbidity, cephalin flocculation, serum bilirubin, nonprotein nitrogen, and serum calcium were normal. Urinalyses revealed from 1 to 20 red blood cells per high-power field. Gastric analysis revealed no free hydrochloric acid until one and one-half hours after alcohol stimulation, and then there was only 8 units. Chest x-ray and fluoroscopy revealed left ventricular hypertrophy and pleural thickening but no evidence of arteriovenous aneurysm. An upper gastrointestinal series revealed a normal functioning anastomatic site, with no evidence of ulcer. Electrocardiogram revealed myocardial abnormality on basis of T-wave changes and frequent premature auricular contractions. Renal biopsy revealed changes diagnosed as acute glomerulitis, with no evidence of telangiectasia of the renal tissue.

On the night of admission blood transfusions were started, and over the following 36 hours the patient received 2,500 cc. of whole blood. Topical thrombin, 300 units orally in milk every two hours, was given during the first two days. He also received large doses of vitamin K_1 oxide, ascorbic acid, and natural vitamin P complex and ascorbic acid preparation (C. V. P.) during the first two weeks. On this therapy the patient's hematocrit level rose to 40% and became stable and his stools became brown and only 1 to 2 + positive for occult blood. The value of any of the medication other than the blood transfusions is difficult to evaluate, because the patient had recovered from his prior episodes of hemorrhage quite promptly with bed rest and blood transfusions alone.

The day after admission, when the patient's status was improved, further questioning about his telangiectasia revealed the following: He had first noted the lesions on his lip when he was about 15 years old and thought they had become more prominent since then. He had had several episodes of brisk bleeding from the larger lesions from such minor trauma as eating hard food or allowing the lips to chap, and this bleeding was often difficult to stop. He denied epistaxis at any time. Family history revealed that the patient's grandfather had similar lip lesions, which often bled rather profusely. His mother and two aunts had similar lip lesions but no known hemorrhage from them. Two brothers had lip lesions, one brother having frequent bleeding and the other being asymptomatic. The four-generation family tree is shown in Figure 2, with the uninvolved members represented by plain blocks, those with lip lesions but no hemorrhage represented by cross-lined blocks, and those with lip lesions and hemorrhage represented by diagonally lined blocks. Only the patient, one brother (Fig. 3), and one of patient's sons were available for examination by us. The brother had had a subtotal gastric resection for peptic ulcer two years previously for intractable pain. He had had no known gastrointestinal bleeding. There was no family history of epistaxis.

At this point, the diagnosis of hereditary hemorrhagic telangiectasia seemed established, but whether the patient's gastrointestinal bleeding was unrelated to this disease or due to telangiectatic involvement of the gastrointestinal tract was as yet not known. Information from the pathologist at the hospital where the gastric surgery was performed revealed the specimen to consist of 50 to 60% of the stomach. The serosal surface contained a few dilated superficial vessels. There were a few 1 to 3 mm. superficial ulcerations near the pylorus on the lesser curvature, which on section did not

Fig. 4.—Artist's drawing of gastroscopic view of stomach.



extend deeper than the submucosa. The microscopic slides were not available for review.

Proctoscopy and esophagoscopy both revealed normal mucosa, with no evidence of telangiectasia. Gastroscopy performed 14 days after admission revealed a normal stomal opening and normal mucosa. However, in the anterior aspect of the stomach three bright red 2 to 4 mm. lesions were seen. Nearby was a larger lesion, from which blood was dripping.

Three weeks after admission, while the patient was taking a bland diet, antacids, antispasmodics, and mild sedation and was semiambulatory, asymptomatic, and maintaining a stable hematocrit level (but still having 1 to 3 + ocult blood in his stools), he rather suddenly developed nausea, abdominal "fullness" and weakness and a few hours later had an emesis of about 1,200 cc. of coffee-grounds-like material. Within a few hours, his hematocrit level dropped from 42 to 34 vol. %. He was given 1,000 cc. of whole blood and was again given topical thrombin, 300 units in milk orally every three hours for two days. The patient had no further vomiting, and by the following morning he was feeling stronger and looked less pale and his hematocrit level was 37 vol. %. One week later, because of a gradual drop of his hematocrit level to 34 vol. %, he was given a 500 cc. blood transfusion. At this time also he was started on a regimen of vitamin K, 20 mg.; ascorbic acid, 100 mg., and rutin, 40 mg. three times daily. During the following week his hematocrit level gradually rose to 41 vol. % without further transfusions and his stools revealed less occult blood, on two days being negative. Then, without any apparent provocation, and while still taking the above medication, the patient began to pass tarry stools, and in the following two days his hematocrit level fell from 40 to 34 vol. %. At this time repeat gastroscopy was performed. At this examination lesions similar in appearance but more numerous than on the first examination were seen. Fresh blood was seen trickling from several of these lesions (Fig. 4).

Fig. 5.—Photograph of stomach remnant immediately after excision.

Adrenochrome monosemicarbazone sodium salicylate complex (Adrenosem), 5 mg. intramuscularly every two hours for five doses, was added to the patient's regimen. One day later the same dose was started every four hours and given for two days. Then 2 mg. was given orally four times daily. The patient also received a 500 cc. blood transfusion However, the patient's stools continued to contain occult blood and it was felt that this medication was

not effective in stopping his bleeding. Since almost every known medical regimen had been tried without success in controlling the patient's gastrointestinal hemorrhage, it was the consensus of opinion that total gastrectomy should be offered the patient as a last resort, with the realization that the patient was not a good surgical risk and also that there could well be bleeding telangiectasia in the small or large intestine that could not be visualized by endoscopy. The problem was presented to the patient, and he accepted surgery. In March, 1954, surgery was performed. When the stomach was opened there were several 1 to 3 mm. reddened vascular-appearing areas in the mucosa and one deep red nodular mass 1 cm. in diameter near the old anastomosis line. All except a very small cardiac cuff of the stomach was removed, and this was anastomosed to a loop of jejunum. After the stomach remnant had been removed, the vascular

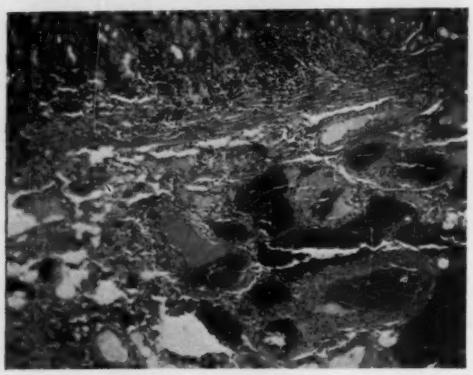


Fig. 6.—Photomicrograph of stomach wall, showing vascular dilatations.

markings on the mucosa were much less apparent (Fig. 5). Pathological examination revealed numerous foci of prominent mucosal capillaries throughout. The nodular mass was considered to be a foreign-body reaction from an old suture. In the submucosa there was dilatation of existing vessels as well as the formation of new vascular spaces. These changes were interpreted as consistent with hereditary hemorrhagic telangiectasia by the Armed Forces Institute of Pathology (Fig. 6).

The patient withstood the procedure well, receiving 1,000 cc. blood during and after the procedure. During his early postoperative course he had difficulty eating because of abdominal pain and could eat only small quantities, which was considered consistent with the course expected for a postgastrectomy patient. His hematocrit level remained stable until 11 days after operation, when he passed tarry stools, vomiting a small quantity of dark blood, and became weak and his hematocrit level dropped from 39 to 27 vol. % in two days. The patient was given 500 cc. of fresh blood daily for a total of eight transfusions and his hematocrit level gradually rose to 45 vol. %, but about 13 days after the first postoperative hematemesis the patient had another hematemesis and his hematocrit fell to 35 vol. %.

At this point the patient was returned to the medical service for further follow-up management. Because hormonal (estrogen-androgen) therapy had recenty been reported [21] to be effective in treating hemorrhage from hereditary hemorrhagic telangiectasia of the nasal mucous membranes, it was decided to try corticotropin (ACTH) empirically, and in April, 1954, corticotropin-gel (Acthar-gel) was started, using 80 units intramuscularly daily for two days and then 40 units daily thereafter. He was also given two more blood transfusions. The patient's hematocrit level rose to the mid-40's, where it remained stable for almost two months without further transfusions. During this time there was no hematemesis but the stools always contained occult blood. The patient received vitamin B_{12} intramuscularly and ferrous gluconate orally.

The patient's gastrointestinal symptoms then became the main and a very baffling problem. He had a severe postgastrectomy syndrome, with more pain than is usually encountered, and the pain was only slightly responsive to numerous medications and diet adjustments. Repeat gastrointestinal series failed to reveal any evidence of ulceration or obstruction. Results of barium enema and gall-bladder studies and serum amylase and repeat liver-function studies were within normal limits.

After 15 days of corticotropin at 40 mg. daily, the dose was gradually reduced over the following month and then discontinued. Concomitant with the discontinuance of corticotropin, the patient's hematocrit level began to fall, reaching a level of 30 vol. % in about a week, and the patient began to notice purplish blood in his stool but had no hematemesis. Over the following two-week period the patient received sixteen 500 cc. blood transfusions, with variation in his hematocrit level from day to day but with no net rise. During this time all his stools were tarry and purplish, with some red blood. A Cantor tube was inserted and aspirations were made at various levels until blood-containing fluid was obtained, to determine the highest level of bleeding. At 83 cm. from the nares a brownish fluid was obtained which was strongly positive for occult blood. X-ray of the abdomen revealed the tip of the tube to lie in the midjejunum. Corticotropin in dosage of 30 mg. and then 40 mg. daily and also ascorbic acid, vitamin K, and rutin were reinstituted, but they were without apparent effect on the bleeding for about two weeks, after which the hematocrit level stabilized but the stools remained strongly positive for occult blood.

In June, 1954, the patient had an episode of bleeding from his lip telangiectasia, this being his only episode of this during his hospitalization. There was no known initiating trauma. Blood loss amounted to about 50 cc., and the hemorrhage stopped spontaneously.

Because of the patient's increasing restlessness and discouragement from prolonged hospitalization, he was allowed to go home under the care of his private physician in July, 1954. To the time of this report no significant changes in the patient's status have occurred.

COMMENT

This patient portrayed several of the typical manifestations of heriditary hemorrhagic telangiectasia: (1) family history of similar lesions, (2) characteristic-appearing lesions (though not in nasal mucous membranes), (3) increase in bleeding from telangiectasia with increasing age, (4) no discernible abnormality in blood clotting ability, and (5) inapparence of the lesions when the involved tissue is excised from its blood supply. He also portrayed several atypical features: (1) absence of epistaxis at any time, (2) no discernible lesions of the anterior nasal mucous membranes, and (3) strongly positive tourniquet (Rumpel-Leede) test.

On admission this patient represented a problem of recurrent severe gastrointestinal hemorrhage, the etiology of which had been unrecognized for at least a year, in spite of frequent medical attention. This is understandable in view of the fact that the patient never had the most typical symptom of hereditary hemorrhagic telangiectasia, i. e., epistaxis (in contrast to most of the previously reported cases with gastrointestinal hemorrhage, in which nose bleeds were usually a prominent feature) and also because his lip and mouth lesions never bled concomitantly with his gastrointestinal hemorrhage. However, this case indicates that this hereditary anomaly should be considered in the differential diagnosis of all unexplained gastrointestinal hemorrhage.

The value of endoscopic examination is portrayed in this case, in that telangiectasia cannot be demonstrated by barium studies. The spontaneous onset and cessation of hemorrhage, which is typical of this disease, makes evaluation of therapy extremely difficult, a fact well-depicted by this case report. Several medications seemed to be effective at one time but proved to be of equivocal or no value at other times. None of the medications, including corticotropin and some which have been advocated as helpful by other authors, was of any definite value.

The possibility of widespread distribution of the telangiectasia in this disease must be kept in mind in arriving at a diagnosis and also in planning therapy. Our patient apparently has lesions in the small, and possibly in the large, intestine, in addition to lip and gastric lesions, judging from postoperative hemorrhage. This was accepted as a strong possibility before gastric resection, but it was felt that removal of the known bleeding lesions of the stomach was necessary in an attempt to prevent or diminish further massive hemorrhage. Although this patient was not appreciably benefited by total gastrectomy, since melena has continued, the repeated hematemeses have been terminated. The persistent abdominal discomfort since total gastrectomy has been distressing, and its reason, obscure.

SUMMARY

A discussion of hereditary hemorrhagic telangiectasia is presented, with a review of the literature of those cases with gastrointestinal involvement.

A case with gastrointestinal involvement with severe hemorrhage is presented.

The difficulties and unsatisfactory status of present medical and surgical therapy of this condition are portrayed.

The value of endoscopy is demonstrated.

The necessity of considering hereditary hemorrhagic telangiectasia in the differential diagnosis of gastrointestinal hemorrhage of unknown etiology is emphasized.

Victor Landy and Larry Gaskins, of the Medical Illustration Laboratory, Veterans Administration Hospital, Washington, D. C., provided the photographic material, and Phyllis Anderson, of the Medical Illustration Laboratory, Walter Reed Army Medical Center, provided the artist's drawing used in this paper.

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CLINICAL COMPARISON OF VITAMIN K_1 AND WATER-SOLUBLE VITAMIN K

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AS ORAL anticoagulant therapy has become more widespread the hazard of associated bleeding has increased; today bishydroxycoumarin (Dicumarol) and similar preparations are common causes of drug intoxication.[1] This serves to emphasize the importance of effective antidotes to combat hypoprothrombinemia so induced. The comparative effects of oil-soluble vitamin K_1 and the water-soluble vitamin-K-like preparations (synthetic naphthoquinones) in correcting such hypoprothrombinemia is the subject of this paper. Their relative effectiveness in correcting prothrombin deficiency due to other causes is also discussed.

Dam first described a deficiency state in the chicken similar to scurvy, not prevented or cured by ascorbic acid, characterized by a marked prolongation of the clotting time, which he ascribed to a lack of a particular antihemorrhagic factor—vitamin K, which was fat-soluble.[2] Subsequent work by Quick and his group established the relationship of vitamin K deficiency and hypoprothrombinemia. In 1939 Fieser synthesized vitamin K_1, identical with the natural vitamin K, but owing to difficulty in preparation its clinical use has been limited. A satisfactory emulsion is now available for oral or intravenous usage.* More readily available have been the synthetic water-soluble naphthoquinones (menadione sodium bisulfite, U. S. P. [Hykinone]; sodium menadiol diphosphate [Synkavite sodium diphosphate]) possessing vitamin K activity, and these have been most commonly used to correct excessive hypoprothrombinemia. Much confusion has existed between these two groups of preparations. Fieser, commenting on the popular misconception that the family of K vitamins includes a host of individual substances, emphasized that the known list of natural antihemorrhagic factors includes only K_1, from alfalfa, and K_2, from putrefied fish liver.[3] Water-soluble vitamin K preparations are but synthetic naphthoquinones possessing some vitamin-K-like activity. Miller, Harvey, and Finch explain the important difference between the two preparations on the basis of the phytyl group present in vitamin K_1.[4] Many reports † have appeared concerning the clinical use of these preparations. Generally it is felt that the synthetic naphthoquinones are unreliable in correcting hypoprothrombinemia produced by oral anticoagulant therapy.

METHODS

The Quick one-stage prothrombin test, employed for routine clinical purposes in the University Hospital, was used in the following studies. The prothrombin activity of the patient's blood is expressed in terms of per cent of normal prothrombin concentration as derived from a standardized curve. One hundred per cent concentration is equivalent to a prothrombin time of 12 seconds; 30% concentration, to 22 seconds; 15% concentration, to 30 seconds. Bleeding on the basis of hypoprothrombinemia rarely occurs at a concentration above 30 to 40%, and it has been the purpose of vitamin K therapy to restore the prothrombin to this or higher levels.

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This study was assisted by a grant from the H. H. Rackham School of Graduate Studies at the University of Michigan. Supplies of phenindione (Indon) and diphenylacetyl-1,3-indandione (Dipaxin) were made available through the courtesy of Parke, Davis & Company and the Upjohn Company, respectively.

* Mephyton (Merck & Company, Inc.).

† References 5-8.

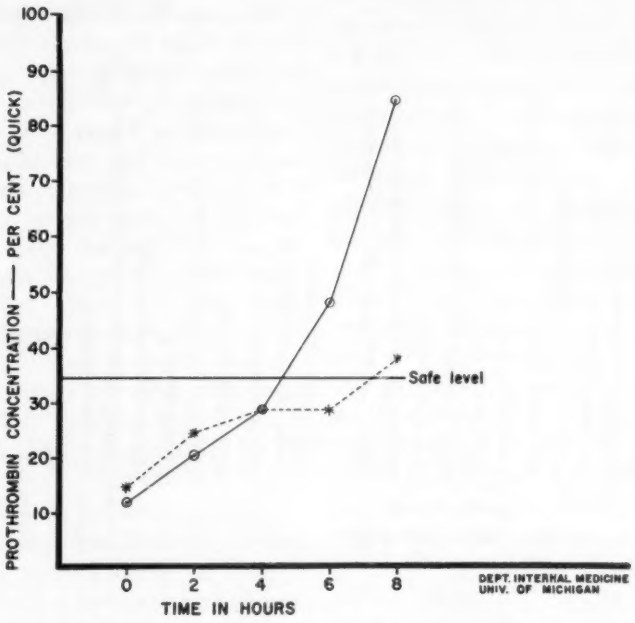

Fig. 1.—Prothrombin response to orally administered water- and oil-soluble vitamin K in a single person. Dotted line, response to 72 mg. menadione sodium bisulfite; solid line, response to 5 mg. vitamin K_1 (Mephyton).

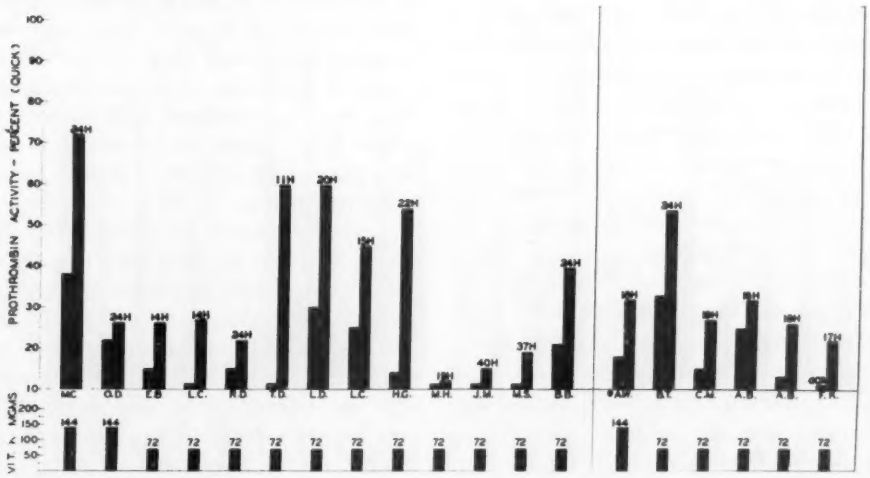

Fig. 2.—Prothrombin response to intravenous adminstration of water-soluble vitamin K (menadione sodium bisulfite). Patients in the first group received bishydroxycoumarin; those in the second group received phenindione. The asterisk indicates patient who received blood to combat blood loss.

RESULTS

To compare the effect of a small oral dose of vitamin K_1 on the known prothrombin response of a single patient, a 62-year-old man with rheumatoid arthritis was given a course of phenindione (phenylindandione) ‡ to reduce the prothrombin activity below 20%, and the recovery time was evaluated. When recovery was complete, a second course of phenindione was given until the prothrombin activity was below 20%, when 72 mg. of menadione sodium bisulfite, U. S. P., was administered orally (Fig. 1). The rise in prothrombin concentration was determined at 2-hour intervals, with a safe level (42%) not occurring for 12 hours; the level was 51% in 24 hours. A subsequent course of phenindione was given to depress the prothrombin concentration to 12%, at which time 5 mg. of vitamin K_1 given orally produced a rise of prothrombin concentration to 49% in six hours, 85% in eight hours. In both instances, at least 250 mg. of phenindione had been administered in the 24 hours preceding the doses of vitamin K.

The prothrombin response to intravenous water-soluble vitamin-K-like substance in a group of patients under treatment with either bishydroxycoumarin or phenindione is shown in Figure 2. The prothrombin activity in per cent is shown in the vertical columns, with the dose of menadione sodium bisulfite below in each case. The first column in each case shows the initial prothrombin level, with the second column indicating the response after administration of the menadione sodium bisulfite; the time interval is indicated in hours at the top. In the group receiving bishydroxycoumarin, the drug had been discontinued from one to seven days before treatment with menadione sodium bisulfite. Phenindione had been given 24 hours or less before menadione sodium bisulfite. In our complete series—not all shown here—only 14 out of 32, or less than 50%, showed a return to safe prothrombin levels in 24 hours or less. It is evident that the response to menadione sodium bisulfite is unpredictable and unreliable.

The prothrombin response to intravenous vitamin K_1 in 27 patients being treated with bishydroxycoumarin, phenindione, or diphenylacetyl-1,3-indandione (Dipaxin) is summarized in Figure 3. In these examples all the patients had received phenindione less than 24 hours before administration of vitamin K_1, although several days may have elapsed after the last dose of Dipaxin. In every case an adequate response was obtained in 4 to 24 hours. It is probable that the response occurred sooner than the longer intervals tabulated, but this was the first determination after the vitamin K_1 was given. It can be seen that even with the small 5 to 10 mg. doses the prothrombin concentration returned to safe levels.

Figure 4 shows the prothrombin response to oral vitamin K_1 in 21 patients under treatment with phenindione or Dipaxin. Here two failures are noted: W. L., who showed no response in 24 hours after 25 mg. of oral vitamin K_1, was found to have gastric dilatation and obstruction and promptly responded satisfactorily to 25 mg. of intravenous vitamin K_1; M. E. showed a poor response to 10 mg. of oral vitamin K_1 at 17 hours but was a patient who had an initial prothrombin level of 43% associated with chronic congestive heart failure. At the end of 48 hours the prothrombin concentration had returned to pretreatment levels. Thus, even with small oral doses of vitamin K_1, a prompt return to a safe level can be obtained. This has the definite advantage of permitting early resumption of anticoagulant therapy, if such is contemplated. With the small doses used, therapeutic levels can be reestablished in as little as 24 hours. Our most recent experience has shown that, in a patient whose prothrombin level is undesirably prolonged, 1 mg. of oral vitamin K_1 will produce a level which is safe yet still within the therapeutic range. This patient, who not uncommonly is very sensitive to oral anticoagulants, can be continued on treatment and easily treated with vitamin K_1 in 1 to 2 mg. oral doses so

‡ Indon (Parke, Davis & Company).

that a therapeutic prothrombin concentration is maintained. If bleeding should be severe enough to produce shock, whole blood or plasma transfusions should be administered as indicated.

thrombinemia due to causes other than anticoagulant therapy. These have been somewhat arbitrarily divided into those with and those without severe hepatic disease. Figure 5 shows the responses to intravenous water-

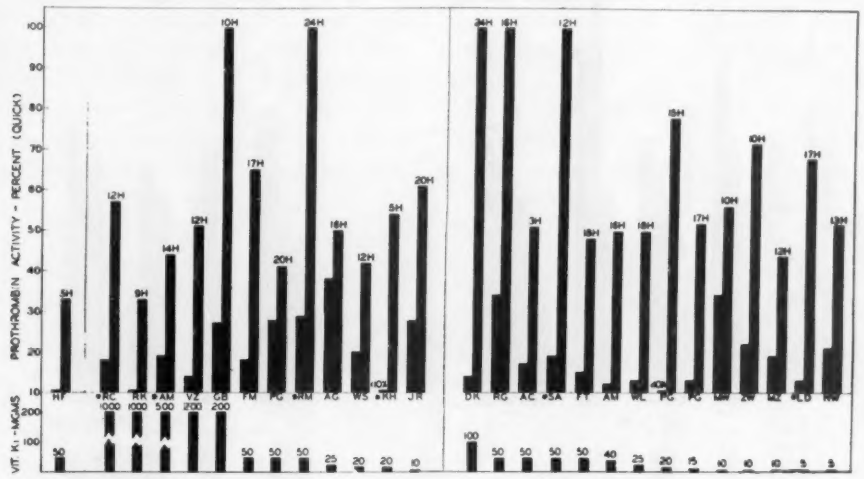

Fig. 3.—Prothrombin response to intravenous administration of vitamin K_1. Patients in the first group received bishydroxycoumarin; patients in the second group received phenindione; patients in the third group received diphenylacetyl-1,3-indandione (Dipaxin). Asterisks indicate patients who received blood to combat blood loss.

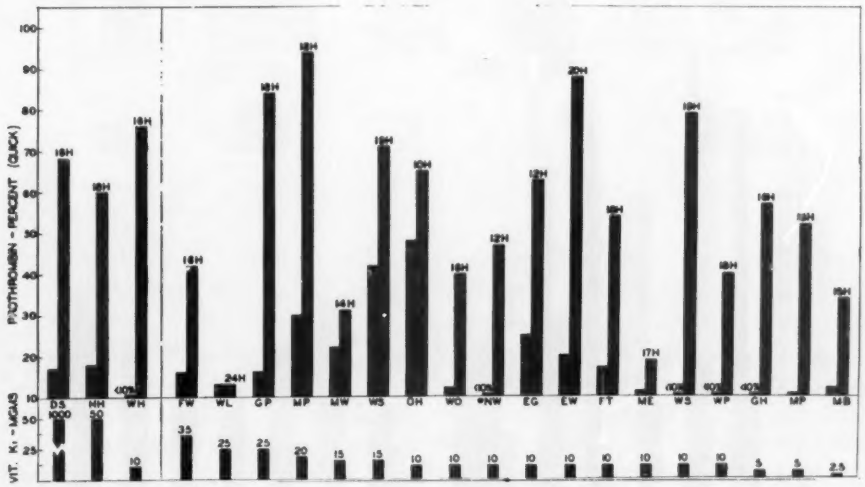

Fig. 4.—Prothrombin response to orally administered vitamin K_1. Patients in the first group received phenindione; patients in the second group received Dipaxin. Asterisk indicates patient who received blood to combat blood loss.

Comparison has been made of the effect of the water-soluble vitamin-K-like substances and vitamin K_1 in patients with hypoprothrombinemia due to causes other than anticoagulant therapy. These have been somewhat arbitrarily divided into those with and those without severe hepatic disease. Figure 5 shows the responses to intravenous water-soluble vitamin K in representative groups of patients. Among those without severe hepatic disease, O. M. had obstructive jaundice

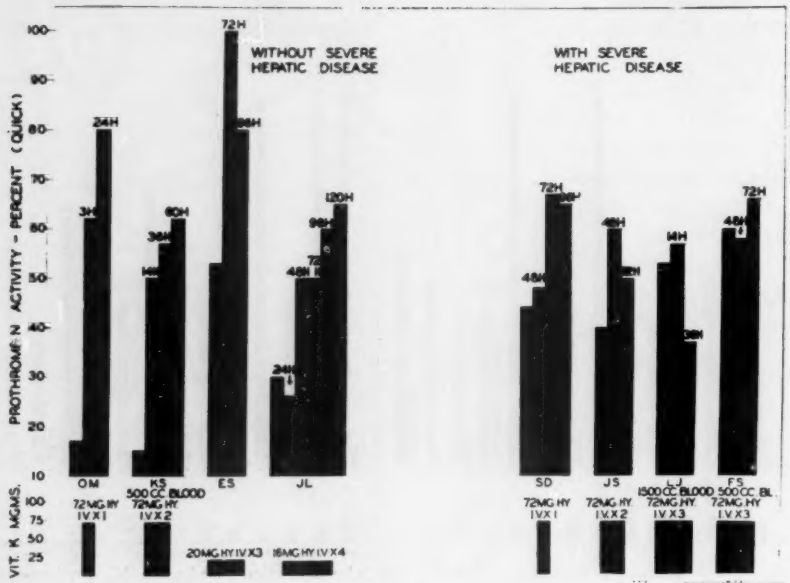

Fig. 5.—Prothrombin response to water-soluble vitamin K (menadione sodium bisulfite) (patients not given anticoagulants).

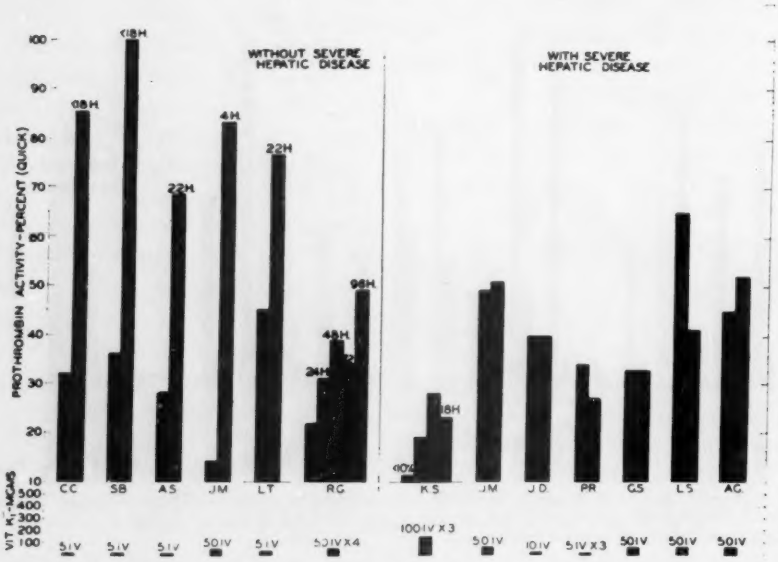

Fig. 6.—Prothrombin response to vitamin K_1 (patients not given anticoagulants).

due to carcinoma of the head of the pancreas; K. S. had ulcerative colitis with peritonitis; E. S. had epistaxis which cleared after vitamin K therapy, and J. L. had a subdiaphragmatic abscess. Each showed a satisfactory response to the administration of the indicated doses of vitamin K. Of the four patients with severe hepatic disease, the first three—S. D., J. S., and L. J.—had extensive liver metastases from colonic carcinoma; F. S. had obstructive jaundice due to a stone in the common bile duct. It is evident that prothrombin to a level compatible with surgery after repeated 50 mg. doses on successive days.

In the group with severe hepatic disease, either atrophic cirrhosis of the liver or extensive metastatic liver disease was present. K. S. had an initial prothrombin time of greater than 180 seconds, and her prothrombin rose to 20 to 30% after three 100 mg. doses of intravenous vitamin K_1, although no further rise occurred. The other patients showed no response at all, some showing a

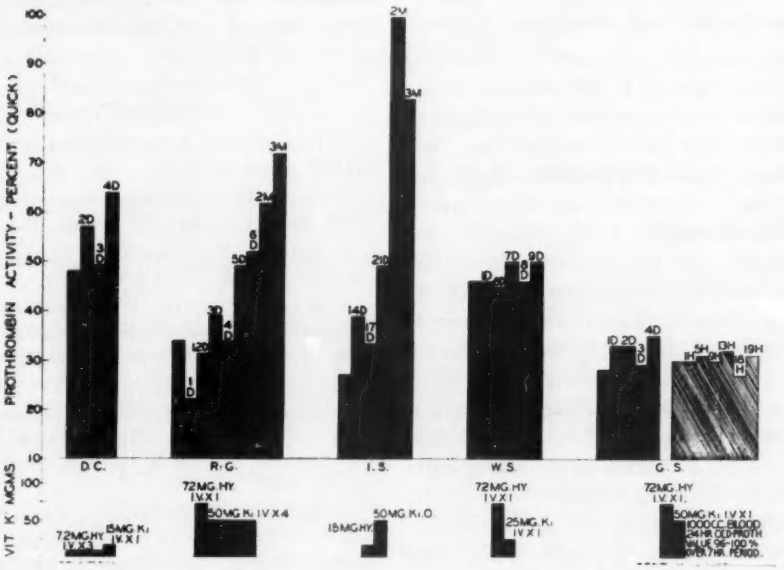

Fig. 7.—Effectiveness of water- and oil-soluble vitamin K in hypoprothrombinemia secondary to severe liver disease.

even repeated doses of menadione sodium bisulfite were not very effective in raising prothrombin levels.

The response to the indicated dose of vitamin K_1 in similar groups of patients is shown in Figure 6. Here, C. C., S. B., J. M., and L. T. all had obstructive jaundice, due to carcinoma of the head of the pancreas or a stone in the common duct. A. S. had a perforated duodenal ulcer with peritonitis. Each responded dramatically in as short a time as four hours to as little as 5 mg. of vitamin K_1 intravenously. R. G. had chronic constrictive pericarditis and showed a gradual rise of decreased value, which was observed to be a particularly ominous sign.

Water-soluble vitamin K and vitamin K_1 were each given to the same patients with severe liver disease, and comparative results are shown in Figure 7. D. C. had chronic congestive failure due to pulmonary stenosis and showed an inconstant response to menadione sodium bisulfite, but vitamin K_1 appeared to be more effective, making cardiac surgery safer. R. G., with chronic constrictive pericarditis, showed no response to one injection of 72 mg. of menadione sodium bisulfite and had a slow significant rise after

repeated doses of vitamin K_1. I. S. had severe unclassified liver disease, with no response to vitamin K or vitamin K_1, although with recovery from the disease normal prothrombin values occurred. W. S., with chronic constrictive pericarditis, showed no response to either preparation. G. S., with hepatolenticular degeneration, had intermittent bleeding, with prothrombin concentrations ranging from 23 to 40%, over a three-year period and showed no response despite repeated attempts to raise the prothrombin level with blood, vitamin K, and vitamin K_1.

SUMMARY AND CONCLUSIONS

The prothrombin responses to water- and to oil-soluble vitamin K preparations in patients under treatment with anticoagulants is compared. It is shown that oil-soluble vitamin K_1 is more effective than any other agent now available in combating drug-induced hypoprothrombinemia. In contrast, the water-soluble vitamin K preparations are unreliable and have an inconstant effect. In most cases vitamin K_1 in doses as low as 1 to 5 mg. orally has been observed to produce as satisfactory a response, in as short a time as four hours, as the large intravenous doses generally recommended. This low dose has the distinct advantage of permitting early resumption of anticoagulant therapy. No refractoriness to subsequent orally administered anticoagulants has been noted after using these small doses, although such has been frequently observed after use of larger doses of vitamin K_1.

In the event of severe bleeding due to oral anticoagulants, intravenous vitamin K_1 in a dose of at least 10 to 50 mg. is recommended in addition to whole blood or plasma transfusions, if the latter are necessary to combat shock. The dose must be individualized, with consideration given to source and severity of bleeding and reason for use of anticoagulant therapy. The smaller dose should be adequate when bleeding is moderate and resumption of therapy is planned. In hypoprothrombinemia due to absorptive difficulties, water-soluble vitamin K substances or vitamin K_1 appear to be equally effective, the latter in amounts as small as 5 mg. intravenously. In patients with jaundice of unknown etiology a 50 mg. intravenous dose is recommended. In those showing a poor initial response, administration of 50 mg. of vitamin K_1 intravenously repeated on successive days may produce a rise to safe prothrombin levels. No untoward effects have been observed to follow the administration of vitamin K_1.

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POSTCHOLECYSTECTOMY ORAL CHOLANGIOGRAPHY

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THE NEW method of visualizing the bile ducts by the oral administration of radiopaque material has proved of diagnostic value in two types of biliary tract conditions previously resistant to any form of roentgenologic diagnostic procedure.[1] These are (1) the apparently nonfunctioning gall bladder, as shown by routine cholecystography, and (2) the postcholecystectomy syndrome,[2] in which only the recently devised intravenous cholangiography with sodium iodipamide (sodium N, N[1]-adipyl-bis[3-amino-2, 4, 6-triiodobenzoate]; Biligrafin; Cholografin) has been of diagnostic value.[3-3e]

In patients showing no visualization of the gall bladder in the cholecystograms, oral cholangiograms have shown in some cases visualization of the gall bladder, at times with stones. In the nonvisualized gall bladder with cystic duct obstruction, it has been possible by oral cholangiography to visualize pathologic common bile ducts, sometimes with stones. In the postcholecystectomy syndrome, there have been revealed pathologic dilated common bile ducts, common duct stones, and other pathologic conditions, such as retained cystic duct or gall bladder remnants.[1] In the present review of 106 oral cholangiograms, visualization of the bile ducts has been made possible by the use of a double dose of a high-iodine-content (66.7%) radiopaque substance, iodopanoic acid (Telepaque *).† The principles which have made the procedure successful have been a preliminary period (12 hours) of dehydration, the subsequent use of camphorated opium tincture (paregoric) to induce a sustained spasm of the common duct sphincter, and the taking of serial films at hourly intervals. Following visualization of the bile ducts, an effort is made to differentiate between functional disorders and organic diseases by giving an inhalation of amyl nitrite or a fat meal and taking a final film 30 minutes later.

There have been few improvements in cholecystography since its introduction in 1924.[6] Chief among these has been the use of radiopaque compounds of higher iodine concentration, giving a more intense gall-bladder shadow.[5] With these compounds, the bile ducts often are visualized following the contraction of the gall bladder in response to a fat meal.‡ Following cholecystectomy, routine cholecystograms have occasionally shown remnants of the cystic duct.[8]

All other procedures for visualizing the bile ducts have involved surgical procedures. These usually have been the introduction of dye into the common duct by needle, "T" tube, or catheter.§ The bile ducts also have been visualized by the use of a peritoneoscope, introducing dye into the gall bladder by a needle.‖ The use of intravenous cholangiography has been noted.

In the absence of the concentrating function of the gall bladder or bile fistula, oral cholangiography affords to date the safest method of visualizing the bile ducts. The obvious advantages of an oral procedure include the elimination of the inconvenience, expense, and risk involved in any surgical or intravenous procedure.

TECHNIQUE

Investigations are being conducted to determine the optimum interval between the administration of

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* Made by Winthrop-Stearns, Inc.

† References 4 and 5.

‡ References 4 and 7.

§ References 9 and 10.

‖ References 11 and 12.

the dye and the taking of films. Chemical determinations of the amount of iodopanoic acid in hourly bile specimens of 14 patients with T tubes have been performed, and the results are discussed in the next section.

Dehydration is obtained by withholding all liquids for 12 hours preceding the x-ray examinations except for a glass of hot water with each dose of dye.

A double dose of dye is used in all cases. This is given either the evening before or the morning the films are taken.

Camphorated opium tincture is given two hours after the dye.

Optimal routine procedures now in use are

Dye	Camphorated Opium Tincture	Films Taken
(1) 7 p. m.	drams ii (7.78 gm.) 10 p. m.	9, 10, 11 a. m.; 12 noon
(2) 7 a. m.	drams ii (7.78 gm.) 9 a. m.	11 a. m.; 12, 1, 2 p. m.

After visualization of the bile ducts, an inhalation of amyl nitrite and/or the ingestion of a fat meal are given, and a film is taken 30 minutes later.

The cholangiogram is interpreted on the basis of the following diagnostic criteria:

Visualization:	None, faint, fair, or good
Dilatation:	None, up to 7 mm. Slight, 7 to 10 mm. Moderate, 10 to 20 mm. Marked, over 20 mm.
Pathology:	Stones, organic obstruction, cystic duct remnants, retained gallbladder remnant, etc.
Emptying:	Degree after amyl nitrite or fat meal

CHEMICAL STUDIES

The morning and evening schedules for the examination as outlined were arranged empirically, as the best films were obtained at 5 hours and 14 hours after the administration of the dye. To study the fundamental factors involved and to determine the optimum schedule, a series of patients with T tubes were given a double dose of iodopanoic acid and the hourly excretion of dye was measured chemically.

The maximum excretion was found to occur at 5 hours in some cases and at 14 hours in others (Graphs 1 and 2). The reason for the two different time responses is not as yet apparent. The concentration and amount of dye excreted in the bile was greater when the dye given was followed by the ingestion of food.

REPORT OF CASES

The following case reports have been selected as typical of the findings in each of the groups.

The groups studied to date have been as follows:

Controls.—In the group of 42 control tests in patients having no symptoms after cholecystectomy there were 36 women and 6 men. The ages varied from 29 to 76 years. The average age was 55 years.

In view of the generally accepted opinion that the common bile duct dilates after cholecystectomy, an analysis was made of the intervals after operation and the diameters of the common bile duct. The results are shown in Table 1.

TABLE 1.—*Diameter of Common Bile Duct at Various Intervals After Cholecystectomy*

	Under 1 Yr.	1-5 Yr.	6-10 Yr.	11-21 Yr.
Patients, no.	10	7	11	5
Av. diameter of bile ducts, mm.	10	8	12	8

These facts seem to indicate that in patients having no postoperative symptoms the common bile duct shows slight dilatation, which is not progressive (Fig. 1).

CASE 1.—Woman, 53 years of age. Cholecystectomy six years ago. Recurrent duodenal ulcer. No symptoms referable to the biliary tract.

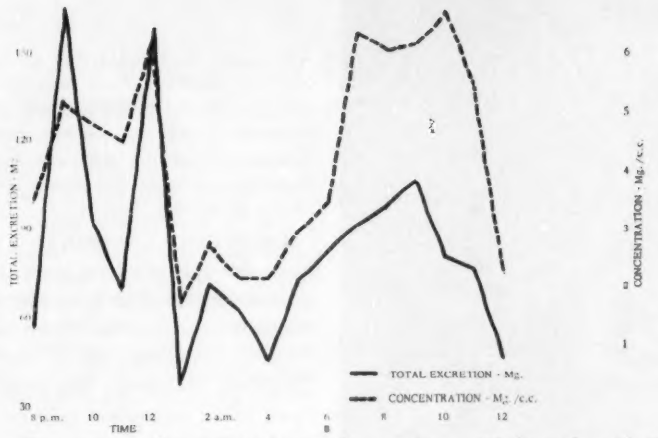
Dyskinesia.—Hypertonic biliary dyskinesia has long been recognized as a factor in producing the postcholecystectomy syndrome.¶ We are in agreement with Colp,[15] who states that it is "a dyskinesia of the common duct sphincter, with which there may be common duct stones, cholangitis, pancreatitis, or a cystic duct remnant."

In this group of 32 patients having postcholecystectomy symptoms, with a clinical diagnosis of dyskinesia, there were 25 women and 7 men. The ages varied between 30 and 80 years. The average age was 47 years.

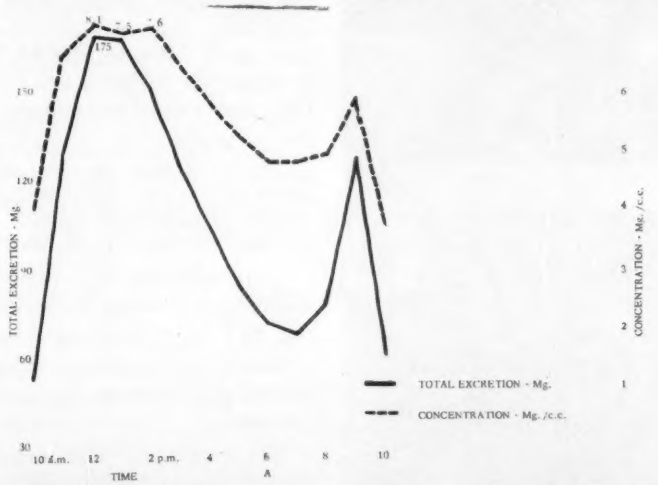
A comparative study of measurements of the common bile duct showed that in the control group only one-third was more than 10 mm. in diameter, whereas in the dyskinesia group two-thirds were over 10 mm. (Fig. 2).

CASE 2.—Woman, 42 years of age. Cholecystectomy 21 years ago. Choledochostomy seven years ago. Findings: Markedly dilated common bile duct

¶ References 2, 13, and 14.



Graph 1.—The concentration and total excretion per hour of iodopanoic acid (Telepaque) as measured in T-tube bile. The dye was administered at 7 a. m. in these seven cases.



Graph 2.—The concentration and total excretion per hour of iodopanoic acid as measured in T-tube bile. The dye was administered at 7 p. m. in these seven cases.

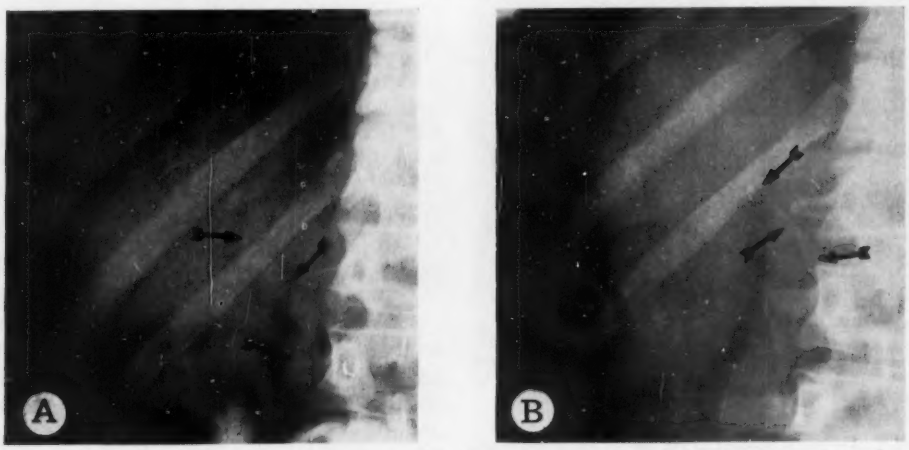


Fig. 1.—Normal appearance of common bile duct, six years after cholecystectomy. *A*, good visualization of duct 7 mm. in diameter. *B*, reduction in size following fat meal.

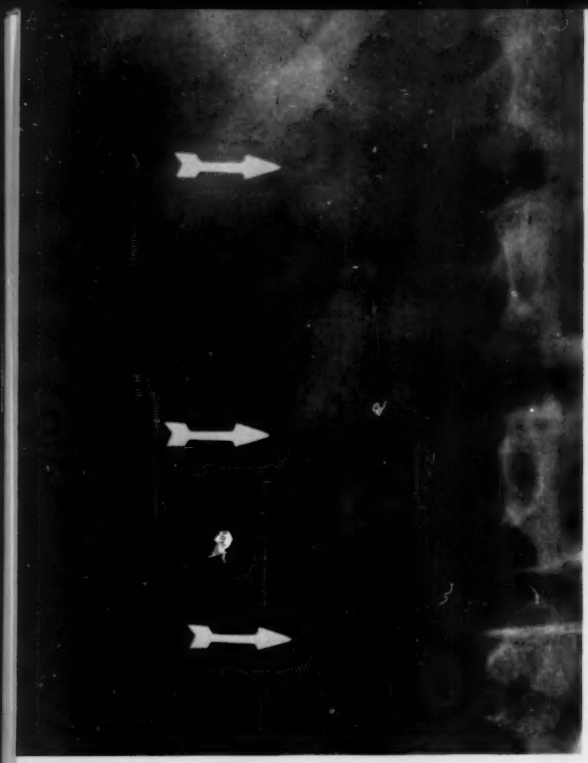


Fig. 2.—Markedly dilated common bile duct, without evidence of stones, in patient having recurrent postcholecystectomy colic. Findings confirmed at operation.

Fig. 3.—Good visualization of common duct and cystic duct remnant, 30 mm. by 90 mm.

with stones. Recurrent attack of right upper quadrant pain, with chills and fever. Cholangiogram revealed markedly dilated common bile duct, without evidence of stones. Operative findings: Markedly dilated common bile duct with hypertrophic common duct sphincter. No stones. (Courtesy of Dr. Henry Doubilet.)

Cystic Duct Remnants.—A retained cystic duct remnant has long been recognized as a possible cause of severe recurrent postcholecystectomy symptoms such as colic, pain, nausea, vomiting, chills, and fever.[16] The diagnosis, however, has usually been confined to an occasional case in which routine cholecystography has revealed the lesion [8] or in which the diagnosis has been made at reoperation.

In each of the six known cases of cystic duct remnant studied in this series, all showed the lesion on oral cholangiographic examination (Fig. 3).

CASE 3.—Woman, 60 years of age. Cholecystectomy 27 years ago. Indefinite digestive symptoms recently. Cholangiogram revealed a dilated common bile duct with retained cystic duct remnant.

Postcholedochoduodenostomy.—Oral cholangiograms were made on four patients having had a choledochoduodenostomy after cholecystectomy, without recent symptoms. In each case there was no visualization of the bile ducts.

In contrast, one patient having symptoms after a choledochoduodenostomy was studied by an intravenous cholangiogram and was found to have multiple hepatic stones. The findings were confirmed at operation.

In one patient in whom there was some question as to whether the original operation had been a cholecystostomy or cholecystectomy, the oral cholangiogram revealed the bile ducts but no cystic duct remnant. At operation there was found a small gall bladder with the cystic duct occluded by a large cholesterol stone.

Retained Gall-Bladder Remnants.—A retained gall-bladder remnant or "reformed" gall bladder may also occur as the result of incomplete surgery.[1] The symptoms are those described for the retained cystic duct remnant. Two patients were studied by oral

cholangiography. Each revealed a shadow similar to that found when no cholecystectomy had been performed. Both patients came to operation; each had a chronically diseased gall bladder. In one, there were several small pigment stones (Fig. 4).

CASE 4.—Woman, 46 years of age. Cholecystectomy 10 years ago. Recurrent attacks of epigastric pain with incisional hernia. Previous cholecystogram revealed no visualization. Cholangiogram revealed good visualization of a gall-bladder remnant. Operative findings: Retained chronically diseased gall bladder, with no stones. (Courtesy of Dr. Charles Gordon Heyd.)

Ductal Lithiasis.—Oral cholangiograms were done in three patients having had previous repeated cholecystographic examination with no visualization of the gall bladder or bile ducts and no evidence of stones. In two of these cases the oral cholangiogram revealed both the gall bladder and the common bile ducts, with multiple calculi in both. The findings were confirmed at operation in each case, one patient having three stones in the hepatic ducts (Fig. 5).

CASE 5.—Woman, 52 years of age. Recurrent attacks of biliary colic for 25 years. Previous cholecystogram showed no visualization. Cholangiogram: Good visualization of the common bile duct, showing multiple calculi. Faint visualization of the gall bladder, with multiple calculi. Operative findings: Diseased gall bladder containing multiple stones. Dilated common bile duct containing seven stones, two stones in the right hepatic duct, and one stone in the left hepatic duct. (Courtesy of Dr. Arthur Localio.)

In the third patient the cholangiogram revealed a cystic duct remnant containing radiolucent stones. This finding was confirmed at operation.

Nonfunctioning Gall Bladder.—Oral cholangiograms were performed in six patients in whom previous routine cholecystograms had revealed no visualization and no stones. In three patients having a patent cystic duct the oral cholangiogram revealed the gall bladder. In one there were no stones. In two stones were visualized both in the gall bladder and in the common duct. In each case the findings were confirmed at operation (Fig. 6).

Fig. 4.—Good visualization of gall bladder remnant, 10 years after cholecystectomy.

Fig. 5.—Good visualization of the common duct containing large calculi. Findings confirmed at operation. Routine cholecystogram previously showed no visualization.

CASE 6.—Chinese woman, 60 years of age. Recurrent attacks of biliary colic since 1929, becoming much severer since 1949. The attacks consisted of right upper quadrant pain radiating to the back.

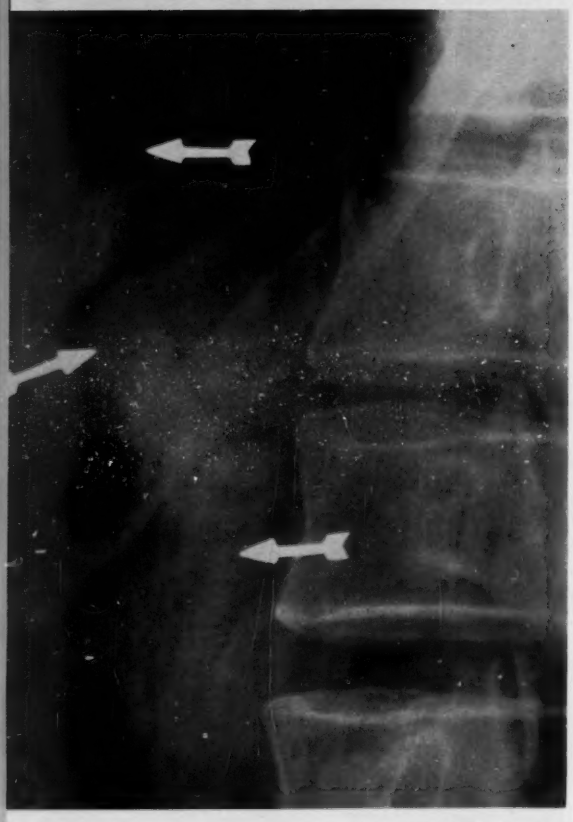


Fig. 6.—Repeated routine cholecystograms with nonvisualization. Oral cholangiogram revealed gall bladder and common duct calculi. Findings confirmed at operation.

Fig. 7.—Good visualization of the common bile duct in a case in which there was no visualization on cholecystographic examination. At operation a widely dilated common bile duct was found, containing two small stones.

She also had indigestion with flatulence and constipation and intolerance to fatty food. She was never jaundiced. Since 1949 she has had repeated gallbladder examinations in various institutions throughout the country, with no visualization at any time. With oral cholangiogram technique fair visualization of the gall bladder and the biliary ducts was obtained. Three calculi were seen in the gall bladder, and a few calculi were seen in the ducts. The ducts were moderately dilated. The findings were confirmed at operation.

In three patients there was a physiological cholecystectomy or organic obstruction of the gall bladder, in each case due to impacted stones. In one of these cases the oral cholangiogram showed no visualization of the bile ducts.

In two cases there was good visualization of a dilated common duct. In one of these no stones were found in the common duct at operation. In the other, two stones about 4 mm. in diameter were found in the common duct (Fig. 7).

Case 7.—Man, 54 years of age. Acute attack of abdominal pain 18 months ago. Laparotomy elsewhere, with diagnosis of acute pancreatitis. Two stones found in the common bile duct, which were not removed. Recurrent attacks of right upper quadrant pain followed operation, one attack with jaundice. Liver and pancreatic function tests were normal. Routine cholecystogram showed no visualization. Cholangiogram revealed a markedly dilated common duct, with a cluster of calcified stones in the region of the cystic duct. Operative findings: a chronically diseased gall bladder containing stones, with the cystic duct obstructed by multiple

Table 2.—*Findings in 106 Oral Cholangiograms*

	Cases, No.	Visualization	No Visualization	Dilatation		
				None	Moderate	Marked
Controls	42	33 (80%)	9	22	11	0
Choledochoduodenostomy (no symptoms)	4	0	4	..	..	..
Dyskinesias	32	24	8	14	7	3
Postcholecystectomy syndrome (cause undetermined)	10	0	10	..	..	..
Cystic duct remnant	6	6	0	1	5	0
Gall bladder remnant	3	3	0	..	..	..
Nonfunctioning gall bladder	6	5	1	..	..	..
Lithiasis	3	3	0	0	2	1
	106	74 (72%)	32	37	25	4

stones. Common duct dilated and containing two stones about 4 mm. in diameter. Liver and pancreas normal in appearance. No common duct obstruction. (Courtesy of Dr. Jere W. Lord and *American Journal of the Medical Sciences*).

SUMMARY

This investigation reviews 106 oral cholangiograms performed by a new technique. The findings in each of the groups are reported.

In 36 comparable intravenous cholangiograms 30 (83%) were visualized.

CONCLUSIONS

Oral cholangiography is a procedure of practical diagnostic value. Visualization of the bile ducts has been obtained in *72%* of the cases in this series. In the control group having no postcholecystectomy symptoms 66% showed no significant dilatation of the common bile duct. Pathologic conditions such as stones and cystic duct remnants have been visualized and proved by operative findings. The percentage and degree of visualization obtained with oral cholangiography are comparable to those of intravenous cholangiography in most cases.

This study was made with the cooperation of the staffs of the University and Roosevelt Hospitals of New York.

Twelve cases were contributed by Drs. Eilif C. Hanssen and Charles Deeb, of the C. M. E. White Memorial Hospital, Los Angeles.

The investigation was aided by a grant from the Irwin Strasburger Memorial Medical Foundation.

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SUSCEPTIBILITY OF NEISSERIA GONORRHOEAE TO ELEVEN ANTIBIOTICS AND SULFADIAZINE

Comparison of Susceptibility of Recently Isolated Strains with Results Obtained in Previous Years in the Same Laboratory

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FOLLOWING the introduction and extensive use of sulfonamide drugs in the treatment of gonorrhea, increasing proportions of treatment failures from the use of these drugs were encountered.* Such treatment failures could be correlated with increased tolerance in vitro to sulfonamides by the strains isolated from the patients who responded poorly to sulfonamide therapy.† Fortunately, both sulfonamide-sensitive and sulfonamide-resistant strains of gonococci were found to be highly and equally susceptible in vitro to penicillin,‡ and infections with strains of both varieties responded equally well to treatment with this antibiotic.§

Increased tolerance to sulfonamides‖ and to penicillin¶ could be induced by prolonged and repeated exposures of originally sensitive strains of gonococci in vitro. However, attempts to demonstrate penicillin-resistant strains of gonococci in cases of failures of penicillin treatment have generally failed,# and the rare reports of the isolation of such penicillin-resistant strains * have been discounted by other observers, who consider the so-called penicillin failures to be due to factors other than the increased tolerance of the gonococcus for the antibiotic.† Studies of the penicillin sensitivity of strains of gonococcus isolated at different times have failed to reveal the appearance of any strains of high resistance or any evidence of a general increase in tolerance for penicillin,‡ although a recent review [24] of this subject cites some workers who have presented evidence that a minor increase in resistance may have occurred which, however, was not of therapeutic significance.

Most of the other antibiotics that have come into general use are active, in varying degrees, against gonococci in vitro, and they have been used, with some success, in cases of gonorrheal infections,[25] either in early clinical trials or in the treatment of patients who were considered to be hypersensitive to penicillin or who had failed to respond clinically to treatment with that antibiotic. To be sure, these antibiotics, like penicillin, have had their widest use in the management of conditions other than gonococcal infections. Nevertheless, in view of the general experience with the increasing resistance of staphylococci to penicillin, chlortetracycline, and oxytetracycline [26] and, more recently, to erythromycin,[27] it is necessary to consider the possibility that such extensive usage may, incidentally, result in the elimination of the strains of many species which are most sensitive to the antibiotics and the concomitant increase in the proportion of resistant strains, even though the treatment with these agents is not primarily directed against infections by the organisms concerned.

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

* References 1-3.

† References 4-7.

‡ References 8-10.

§ References 11 and 12.

‖ References 13 and 14.

¶ References 14-16.

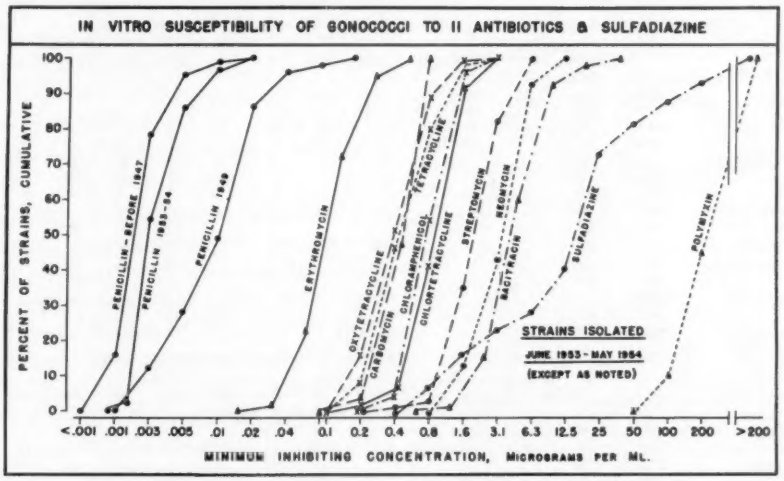
References 17 and 18.

* References 19 and 20.

† References 17 and 21.

‡ References 22 and 23.

The present study is part of a survey of strains of some of the common pathogenic species of bacteria currently being encountered, in an effort to determine whether any significant increases in resistance to the widely used antibiotics can be demonstrated. In this paper are presented the results of tests for susceptibility of recently isolated strains of gonococci to 11 antibiotics and sulfadiazine. These results are compared with similar data obtained in this laboratory with some of the same antibiotics in previous years.§



In vitro susceptibility of gonococci to 11 antibiotics and sulfadiazine.

MATERIALS AND METHODS

The strains of gonococcus used in the present study were obtained between June 28, 1953, and May 3, 1954, from active cases of urethritis in males (92 strains) or cervicitis in females (16 strains). Cultures were made directly on Mueller-Hinton agar [32] promptly after materials were obtained from the lesions; these were done in the genitourinary clinic of the Boston City Hospital by Mrs. Helen Trousdale, who also isolated and identified the strains from single colonies. In this laboratory the strains were maintained by subcultures on slants of either heart-infusion agar (Difco) pH 7.2, to which 10% defibrinated equine blood was added, or on Mueller-Hinton agar.

The antimicrobial agents used and their sources were as follows: sodium sulfadiazine, penicillin G potassium (1 unit considered to be equivalent to 0.6 γ), and streptomycin sulfate were obtained commercially; chlortetracycline (Aureomycin) and tetracycline (Achromycin) were furnished by Dr. Stanton M. Hardy, of Lederle Laboratories Division, American Cyanamid Company; oxytetracycline (Terramycin) and carbomycin (Magnamycin) were supplied by Dr. Gladys L. Hobby, of Pfizer Laboratories, Division of Chas. Pfizer & Company, Inc.; erythromycin (Ilotycin) was provided by Dr. R. S. Griffith, of Eli Lilly & Company; chloramphenicol (Chloromycetin) was obtained from Dr. E. A. Sharp, of Parke, Davis & Company; neomycin sulfate was supplied by Dr. H. F. Hailman, of The Upjohn Company; bacitracin (51.7 units per milligram) was provided by Dr. H. J. Byrne, of Commercial Solvents Corporation, and polymyxin B (Aerosporin) sulfate was furnished by Dr. Donald F. Searle, of Burroughs Wellcome & Company, Inc.

Tests for sensitivity were performed by the two-fold dilution method on the surface of solid media in which the antimicrobial agents were incorporated. Heart-infusion agar was used throughout, except that a few tests with sulfadiazine were also done on Mueller-Hinton agar for comparison. The inoculum was obtained by scraping a generous loopful of a 24-hour growth of the culture from the surface of a blood agar plate and making a uniform suspension of organisms in 1 ml. of broth; a 2 ml. loopful of this suspension was then streaked onto a segment of the surface of each of the series of plates containing the antimicrobials and on a drug-free plate. By serial dilutions and surface-plate cultures, this inoculum was shown to contain about

§ References 23 and 28-31.

10^6 viable organisms. Incubation was carried out at 37 C., with the plates being kept in large desiccating jars containing some water but without CO_2 being added. The plates were inspected for growth after incubation for 48 hours using an engravers lens (× 3). The sensitivity of a strain was defined as the minimum concentration of the antimicrobial agent in the agar plate on which no growth was discernible. The designation "> 400," used in the Table, or "> 200," used in the Figure, indicates growth in a concentration of 400 or 200 γ per ml., respectively, the highest concentrations used, but the course of investigations of other antibiotics are listed in Table 1.

From the Figure it is readily seen that, weight for weight, penicillin was by far the most active of all the antimicrobial agents tested; erythromycin ranked next but was considerably less active. The three tetracycline analogues as well as carbomycin and chloramphenicol were all quantitatively similar in their activity, which was appreciably

TABLE 1.—*In Vitro Susceptibility of Recently Isolated Strains of Neisseria Gonorrhoeae to Eleven Antibiotics and Sulfadiazine: Comparisons with Results Obtained in Previous Years in the Same Laboratory*

			Minimum Inhibiting Concentration, γ/Ml.											
			% of Strains											
Antibiotic	Year	Strains, No.	0.001	0.003	0.005	0.01	0.02	0.04	0.08	0.2	0.4	0.8	1.6	3.1
Penicillin	1945*	24	21	75	4	..	..	..	..	..	..	..	..	..
	1947†	104	16	62	17	4	1	..	..	..	..	..	..	..
	1949†	52	..	13	15	21	37	10	2	2	..	..	..	..
	1954‡	106	2	52	32	11	3	..	..	..	..	..	..	..
Chlortetracycline	1948§	146	..	..	..	..	..	..	3	6	23	39	28	1
	1949	55	..	..	..	..	..	..	4	24	40	30	2	..
	1954	104	..	..	..	..	..	..	..	2	4	34	52	8
Oxytetracycline	1950‖	28	..	..	..	..	..	..	25	68	7	..	..	..
	1954	106	..	..	..	..	..	..	..	16	45	28	10	1
Tetracycline	1954	106	..	..	..	..	..	..	..	8	38	34	19	1
Chloramphenicol	1949	66	..	..	..	..	..	..	..	3	15	64	6	12
	1954	106	..	..	..	..	..	..	..	..	4	49	44	3
Erythromycin	1952¶	10	..	..	..	..	..	..	..	..	20	10	40	30
	1954	106	..	..	..	..	..	1	12	49	23	5	..	..
Carbomycin	1954	51	..	..	..	..	..	..	..	2	45	53	..	..

			Minimum Inhibiting Concentration, γ/Ml.										
			% of Strains										
			0.4	0.8	1.6	3.1	6.3	12.5	25	50	100	200	400	>400
Streptomycin	1949	67	..	6	24	34	34	2	..	..	..	..	..	..
	1954	104	1	2	32	47	18	..	..	..	..	..	..	..
Neomycin	1949	53	..	..	..	..	..	31	30	32	6	0	2	..
	1954	40	..	..	13	30	50	7	..	..	..	..	..	..
Bacitracin	1949	64	..	3	20	23	31	20	3	..	..	..	..	..
	1954	106	..	1	14	45	33	5	2	..	..	..	..	..
Polymyxin B	1949	63	..	..	..	3	6	25	14	14	27	11	..	..
	1954	40	..	..	..	..	..	..	..	..	10	35	30	25
Sulfadiazine	1949	63	..	..	..	..	..	2	0	6	8	5	16	63
	1954	43	..	7	9	7	5	12	33	9	7	5	0	7

* Meads, Ory, Wilcox, and Finland.[28]
† Gocke, Wilcox, and Finland.[28]
‡ Present study.
§ Collins and others.[29]
‖ Gocke, Jackson, Wilcox, and Finland.[30]
¶ Haight and Finland.[31]

it was not determined in every instance whether greater concentrations were actually inhibitory.

RESULTS

The results of the tests for sensitivity of the strains isolated in 1953-1954 are summarized graphically in the Figure. In this figure are also included for comparison some of the results of tests for penicillin sensitivity of strains previously reported from this laboratory.[30] These results and others obtained previously in this laboratory during

less than that of erythromycin. The slightly lower activity of chlortetracycline as compared with its two chemical analogues is probably related to its greater lability under the conditions of these tests. Somewhat less active than the foregoing were streptomycin, neomycin, and bacitracin, in that order. Sulfadiazine was much less active than any of the antibiotics except polymyxin B, which was by far the least active of all the agents tested against the current series of strains.

A few of the recent strains were tested for sensitivity to sulfadiazine on blood agar and on Mueller-Hinton agar simultaneously. The end-points of inhibition with each strain on the two media were either the same or differed by only a single twofold dilution.

Comparisons with Previous Results.—A comparison of the Figure with a similar figure in an earlier publication, which depicts the results obtained with strains isolated in 1949,[23] is of interest. The earlier study included seven of the same antibiotics and sulfadiazine; polymyxin D was included in the previous study but was not used with the recent strains, and erythromycin, oxytetracycline, tetracycline, and carbomycin have all become available after 1949. The order of activity of the agents included in both studies was the same except that in the earlier one sulfadiazine was considerably less active than polymyxin B.

Quantitatively the results obtained with the same antibiotics in the two studies were also quite similar, with some notable exceptions. Sulfadiazine was much less active against the strains tested in the earlier study, whereas penicillin appeared to be slightly more active against the recent strains. This greater activity of penicillin against the strains isolated in 1953-1954 as compared with those obtained in 1949 can be seen from the Figure. This figure also shows the results of tests for penicillin sensitivity of strains studied in 1947 and earlier, which appeared to be more comparable with those obtained with the recent strains. These comparisons are also seen in Table 1, which lists, in addition, the results obtained with the newer antibiotics when they first became available.

Most of the differences noted in the results obtained at different times may be considered to be within the limits of error of the rather crude method used or related to differences in some of the materials used. In particular, the apparently large differences in results obtained in the two studies with neomycin sulfate and polymyxin B may well be due to variations which are known to have occurred in the potency and purity of these products ‖; neither of these agents had been used in any of the patients from whom the strains were obtained nor had they been used in this hospital except on rare occasions. The results of the tests with sulfadiazine, however, showed the recent strains to be inhibited by a much lower and wider range of concentrations, and there was a much smaller proportion of strains of increased resistance as compared with the strains studied in 1949.

Effect of Previous Treatment.—This could be assessed only with respect to penicillin; 23 of the strains of the recent series were from patients who had been treated for acute gonorrhea with penicillin on from one to five occasions prior to the isolation of the strain that was tested. A comparison of the penicillin sensitivity of these 23 strains with that of the 83 strains isolated from patients who denied having previous therapy with penicillin is shown in Table 2. There was no significant difference in the susceptibility of these two groups of strains to penicillin.

TABLE 2.—*Susceptibility to Penicillin of Strains of Gonococcus from Patients Recently Treated for Gonorrhea with This Antibiotic and from Patients Not Previously Treated*

M.I.C.* Penicillin, γ/Ml.	Strains from Patients Recently Treated with Penicillin		Strains from Patients with No Previous Penicillin Therapy	
	No.	%	No.	%
0.002	0	0	2	2
0.003	14	61	41	49
0.005	8	35	26	31
0.01	1	4	11	13
0.02	0	0	3	4
Total	23	100	83	100

* Minimum inhibiting concentration.

COMMENT

The results of the in vitro tests for sensitivity to antimicrobial agents done with the strains of gonococcus isolated in 1953-1954 reaffirm the superiority of penicillin, which has already become well established.[25] They indicate that, in spite of the very extensive use of this agent, both in the treatment of gonor-

‖ References 33 and 34.

rhea and for many other purposes, penicillin-resistant strains of gonococcus probably have not appeared; at least they have not been encountered in this hospital. Nor have the minor variations observed in different years indicated any clear trend toward a significant reduction in the proportion of the most susceptible strains, or increase in prominence of strains of greater resistance, as has been suggested by others.[24]

These findings are in accord with the observations in this and many other clinics where failures of gonococcal infections to respond to treatment with any given dose of penicillin could not be related to increased resistance of the causative gonococcus. Except as already noted,¶ wherever and whenever such cases of penicillin treatment-failures have been studied intensively they have been found to be related either to the use of inadequate doses of penicillin, or to the presence of infection with organisms other than the gonococcus, or to other circumstances. When penicillin-resistant strains of gonococcus are reported, it is essential that the purity and identity of the strain, as well as the results of the tests for susceptibility to penicillin, be carefully and thoroughly confirmed.

The considerably greater susceptibility to sulfadiazine of the strains of gonococcus isolated in 1953-1954 as compared with those studied in 1949 is of considerable interest. In spite of the small numbers of strains tested and the rather wide limits of error of the tests used, the magnitude of this difference appears to be significant. In studies with other bacteria, sulfonamide resistance of individual strains has generally been found to be a stable characteristic of the strains,# although the effect of exposures of such strains to sublethal effects of other agents on their susceptibility to sulfonamides has not been clarified. On the other hand, there is a distinct possibility that a relative reduction in the incidence of strains of high resistance to any given agents (such as the sulfonamides) may take place during periods when these agents are not used, or are used only infrequently, while other agents (such as penicillin), which are highly effective in eliminating such strains, are being widely used. Such a possibility is suggested by the recent experience with erythromycin in one hospital; during a period of five months when that antibiotic was used more extensively than any other the incidence of erythromycin-resistant staphylococci in that hospital rose from 0 to 75%, but the proportion of these erythromycin-resistant staphylococci among carriers dropped to 35% within a brief period after the use of erythromycin was discontinued.[27]

Interpreted literally, the results obtained with sulfadiazine in the two studies at this hospital indicate that about 84% of the strains isolated in 1949 were sulfadiazine-resistant as compared with about 19% of those isolated in 1953-1954—considering strains which are not inhibited by 100 γ per milliliter (10 mg. per 100 ml.) as resistant. Such an interpretation is justified only on two assumptions, namely (1) that a concentration of 10 mg. of sulfadiazine per 100 ml. is readily maintained in blood and tissue fluids—which is justified—and (2) that such a concentration is effective in vivo in eradicating gonococci which are susceptible to that concentration in vitro in the test employed—an assumption which cannot be accepted without further proof.

The findings presented also indicate that the other antibiotics that are generally used for systemic treatment, namely, erythromycin, the three tetracycline analogues, chloramphenicol, streptomycin, and carbomycin, are all active in vitro in concentrations that are readily maintained in the plasma when adequate doses of these agents are administered systemically. Clinical experience, however, indicates that these agents, including erythromycin,[37] are considerably inferior to penicillin in the treatment of patients with gonococcal infections,[25] as they are against the gonococcal strains in vitro. As compared with penicillin, larger doses and longer periods of treatment with the other agents are

¶ References 19 and 20.

References 35 and 36.

necessary for cure, and failures are more frequent.

Comparisons of the results of the in vitro tests with the recent strains and with those obtained in previous years in this laboratory do not give evidence of any change in the pattern of susceptibility of the gonococcus to the antibiotics, other than penicillin, that have been more widely used, namely, streptomycin, chlortetracycline, oxytetracycline, and erythromycin. The data with respect to neomycin appear to indicate a considerable increase in the susceptibility of the recent strains as compared with those tested in 1949, and the reverse appears to be the case with polymyxin B. These differences, in spite of their magnitude, may nevertheless be more apparent than real, since, as already intimated, these antibiotics have shown wide differences in activity of different preparations, and the observed differences may be due to changes in the character and purity of the particular preparations used in the two studies.* The observed differences certainly cannot be attributed to any extensive use of these two agents.

Bacitracin also has not been widely used and is not likely to be used in the treatment of gonococcal infections; its action in vitro suggests that it is not apt to be effective when used alone. Carbomycin, though quite active in vitro, is also not likely to prove highly useful in the treatment of gonococcal infections, because of its poorer pharmacologic properties, particularly the low levels in blood and urine obtainable with maximum tolerated oral doses.†

SUMMARY AND CONCLUSIONS

Strains of gonococcus isolated between June, 1953, and May, 1954, were tested for sensitivity to 11 antibiotics and sulfadiazine in vitro. Weight for weight, penicillin was the most active and erythromycin, though considerably less active, ranked next, followed by the three tetracycline antibiotics, chloramphenicol, and carbomycin, all of which were quantitatively similar in their activity; streptomycin, neomycin, and bacitracin were slightly less active than the foregoing. The strains varied widely in their susceptibility to sulfadiazine, but only about one-fifth of the strains were resistant to 100 γ per milliliter (10 mg. per 100 ml.) by the method employed. Polymyxin B was the least active of the agents tested, none of the strains being inhibited by less than 100 γ per milliliter.

Comparisons with results of tests previously done in this laboratory revealed no evidence of any significant decrease in the incidence of the most sensitive strains or any appreciable increase in the proportion of strains of increased resistance or of the appearance of strains highly resistant to penicillin or to any of the other antibiotics that have been in wide use in recent years, namely, streptomycin, chlortetracycline, chloramphenicol, oxytetracycline, and erythromycin.

There was, however, a much smaller proportion of sulfadiazine-resistant strains and a greater proportion of sulfadiazine-susceptible strains among those isolated in 1953-1954, as compared with those studied in 1949. It is suggested that this may be the result of the marked decrease in the use of sulfonamides and the widespread use of antibiotics, particularly penicillin, in the treatment of gonococcal and other infections or as prophylactic agents.

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FECAL FLORA OF MAN AFTER ORAL ADMINISTRATION OF CHLORTETRACYCLINE OR OXYTETRACYCLINE

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CONFLICTING reports have been published concerning the ability of chlortetracycline and oxytetracycline to reduce the bacterial population of the human intestinal tract. Some investigators consider these drugs useful for this purpose.* In contrast, other workers believe that administration of these antibiotics has only a minor effect on the intestinal flora.† Many of the published studies are concerned with a few fecal cultures on many patients or detailed cultural studies of only a few types of intestinal micro-organisms. The purpose of the present investigation is to make a detailed study of the effect of chlortetracycline and oxytetracycline on the intestinal flora of a few persons in the hope that some of the conflicting opinions may be resolved.

EXPERIMENTAL PROCEDURE

Sixteen normal healthy adult subjects of both sexes were given chlortetracycline orally for a period of five days in a daily dose of 1 gm. (250 mg. four times per day). Three children aged 7, 10, and 12 years who were under treatment for enterobiosis were also studied. These later subjects were given 200 mg. of oxytetracycline orally four times daily for five days.

Fecal specimens were cultured daily in a great majority of the cases for a period of five days before medication, during the course of medication, and following the medication for a varying number of days (up to 25 days), until the fecal flora had returned to normal. Specimens were collected in clean wax-coated cardboard containers and were usually studied immediately. If delay was necessary, the specimens were immediately refrigerated. A sample totaling 1 gm. wet weight was taken from several portions of each fecal specimen and emulsified in 9.0 ml. of sterile distilled water. The mixture was then blended into a homogeneous suspension with a sterile glass rod and 10-fold dilutions were prepared in sterile distilled water. For counting the various micro-organisms or groups of micro-organisms, appropriate dilutions of the specimen were inoculated into the various media given in Table 1. All counts were recorded as numbers of organisms per gram of wet feces.

TABLE 1.—*Culture Media Used for Counting Micro-Organisms*

Organism	Medium	Method of Inoculation
Total aerobes	BBL Eugon agar	Pour plates
Total anaerobes	BBL anaerobic agar	Surface plates
Coliforms	Difco violet red bile agar	Pour plates
Yeasts	Grape juice agar *	Surface plates
Staphylococci	Difco Staphylococcus medium	Surface plates
Streptococci	Difco S F medium	Dilution counts †
Proteus	Difco S S medium	Surface plates
Pseudomonas	Difco S S medium	Surface plates

* The grape juice agar used was prepared by adding 4% agar to commercial grape juice diluted 1:4, mixing, boiling for 3 to 5 minutes, cooling, and pouring into Petri dishes. This medium, with a final pH of 3.9, does not inhibit yeasts and appears to be very selective, permitting only yeasts and other fungi to grow.

† Five tubes of S F medium were inoculated with the appropriate dilution, incubated at 45.5 C., and examined for growth after 48 to 72 hours. From the distribution of tubes showing growth, the "most probable number" for each specimen was determined from the tables of Prescott and co-workers.[14]

Further identification of the total aerobes, the total anaerobes, and the coliforms was not attempted. Representative cultures of yeasts were examined for their ability to produce pseudomycelia and chlamydospores in corn meal agar.[15] Representative strains of Staphylococcus aureus were tested for their ability to produce coagulase, to hemolyze blood, and to ferment mannitol. Occasional cultures of streptococci were identified by Gram stain. Representative cultures of the genus Proteus were identified culturally.[16]

Blood samples were taken from each subject before and at intervals during and after treatment.

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Dr. Maxwell Finland, Boston City Hospital, and Dr. Henry Bakst, Boston University School of Medicine, gave access to a few experimental subjects.

* References 1-8.

† References 9-13.

TABLE 2.—*Duration of Alterations in Fecal Flora Following Medication*

No.	Subjects *	Approximate Number of Days Required by the Organisms to Return to Predrug Levels Following Cessation of Medication						
		Coliforms	Total Aerobes and Total Anaerobes	Yeasts	Total Staphylococcus	Proteus	Pseudomonas	Streptococcus
1	W. L.-I	NS †	17	6	NS	—‡	—	NS
2	E. B.-II	NS	1	0	NS	—	—	NS
3	W. T.	0	0	—	> 3	3§	—	NS
4	V. P.‖	7	13	4§	10	—	—	NS
5	M. P.‖	>13	>13	>13	>13	—	—	NS
6	R. P.‖	0	7	12§	10	—	—	NS
7	R. M.	0	1	0	5	—	5§	NS
8	J. P.-III	3	5	> 5	5	—	—	3
9	A. B.	8	10	8	2	25§	—	17
10	H. B.	3	3	—	12	19	—	7
11	M. S.	10	10	15§	10	15§	—	1
12	W. L.-II	4	4	6	10	6§	—	1
13	J. B.	7	7	9	5	—	—	5
14	M. C.	15	>15	—	>15	15§	—	NS
15	D. L.	0	0	—	0	9§	—	6
16	A. K.	8	8	—	11	17§	—	0
17	A. P.	0	0	—	0	19§	—	0
18	A. C.	0	6	12§	5	—	—	>12
19	K. C.	3	6	—	0	—	—	4
20	T. S.	3	7	—	4	9§	—	> 7

* E.B.-I (treated with chlortetracycline for three days only), J.P.-I (treated with 20 mg. of chlortetracycline daily), and J.P.-II (treated with chlortetracycline intravenously) are not included in the table.

† NS, not studied.

‡ —, organisms not found.

§ Organisms appeared during or following the medication.

‖ Subjects treated with oxytetracycline.

TABLE 3.—*Alterations in Coliform Organisms During and Following Medication*

No.	Subjects	Range of Predrug Counts	Lowest Counts		Highest Counts Following the Decrease	
			Count *	When (Day)	Count *	When (Day)
1	W. L.-I	Not studied	.....	..	.....	..
2	E. B.-II	Not studied	.....	..	.....	..
3	W. T.	6.9×10^8	5.0×10^3	2	2.3×10^8	6
4	V. P.†	1.1×10^7 to 3.7×10^7	No decrease			
5	M. P.†	5.0×10^5 to 2.0×10^6	9.0×10^3	2	1.4×10^8	8‡
6	R. P.†	7.0×10^6 to 3.8×10^7	6.0×10^3	3	1.2×10^8	4‡
7	R. M.	3.1×10^6 to 1.1×10^8	1.6×10^4	3	7.2×10^7	3‡
8	J. P.-III	1.1×10^8 to 1.6×10^8	8.0×10^3	3	5.5×10^8	5‡
9	A. B.	1.2×10^7 to 5.4×10^7	4.2×10^4	4‡	4.6×10^7	10‡
10	H. B.	4.0×10^6 to 3.7×10^7	9.0×10^3	1‡	1.9×10^8	5‡
11	M. S.	4.0×10^6 to 1.7×10^7	1.0×10^5	2	1.6×10^8	3‡
12	W. L.-II	6.2×10^6 to 1.8×10^7	7.0×10^4	2	3.0×10^8	2‡
13	J. B.	1.5×10^5 to 9.0×10^5	1.1×10^4	2	5.0×10^7	3‡
14	M. C.	9.0×10^5 to 5.3×10^6	1.5×10^5	1	2.6×10^8	3‡
15	D. L.	2.0×10^7 to 2.8×10^8	8.0×10^4	5	2.5×10^7	9‡
16	A. K.	5.4×10^6 to 1.2×10^7	6.4×10^5	2	1.7×10^8	5‡
17	A. P.	8.2×10^5 to 1.0×10^7	9.4×10^3	3	1.9×10^7	21‡
18	A. C.	1.3×10^6 to 5.9×10^6	9.0×10^2	2	1.7×10^7	2‡
19	K. C.	8.0×10^5 to 3.0×10^7	Not found	4 to 1‡	2.5×10^8	4‡
20	T. S.	2.1×10^6 to 2.1×10^7	4.4×10^4	4	4.8×10^7	4‡

* Count is the number of coliform organisms per gram of wet feces.

† Subjects treated with oxytetracycline.

‡ After cessation of the medication.

The sera from subjects in whom Proteus developed in large numbers were tested for agglutinins against one strain of the organism isolated from that subject at the time of peak development of Proteus. The antigen used was a saline suspension of the appropriate culture boiled for one hour to remove H antigens. The resulting "O" agglutinin titers were read after 18 hours' incubation at 50 C.

RESULTS

Bacteriological Studies. — Administration of either chlortetracycline or oxytetracycline resulted in a definite alteration in the fecal flora of all subjects. Since chlortetracycline and oxytetracycline behaved in a similar manner, the results for both drugs will be presented together. The duration of changes in the fecal flora is summarized in Table 2.

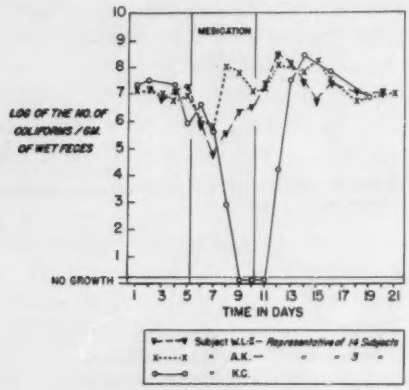

Fig. 1.—Patterns of alteration in coliform organisms.

Generally the alterations in the fecal flora vary considerably from subject to subject as well as from organism to organism. The data presented below will tend to show the common patterns for each group of organisms studied. Some of the results of this investigation have been previously reported.[17]

1. Coliform Bacteria: In this investigation the term "coliform" includes all lactose-fermenting Gram-negative rods. The alterations in numbers of coliform organisms during and following medication are summarized in Table 3 and Figure 1.

The curves in Figure 1 represent data obtained from individual subjects. Similar data were obtained for other subjects. The change generally noted in 14 subjects was a decrease in numbers quickly followed by an increase in coliform organisms. The maximal decrease usually occurred on the second or third day after the start of the medication. The maximal increase in population following the initial decrease occurred in a period from 2 to 21 days after discontinuance of medication. The average was about six days.

Several minor variations in the pattern were also noted. Two subjects (A. B., H. B.) showed a late maximal decrease, which occurred after the medication had been discontinued, in contrast to the early maximal decrease, which occurred during medication, in all the other cases. Four subjects (M. P., W. L.-II, M. S., J. B.) showed increases in numbers of coliform organisms to well above the predrug levels. The other eight subjects showed increases in numbers of coliform organisms only to the predrug levels.

Another pattern of alteration was noted in three subjects (A. K., M. C., V. P.) in whom there was no appreciable change in coliform population throughout the course of study.

In one subject (K. C.) the medication resulted in complete disappearance of coliform organisms from stool cultures. These data are listed separately because similar observations have been reported by other investigators.‡

A period of from 0 to 15 days (averaging about 5 days) following discontinuance of the drug was required for the numbers of coliform organisms to return to their predrug levels (Table 3).

2. Total Aerobes and Total Anaerobes: The term "total aerobes" includes all organisms culturable on Baltimore Biological Laboratory (BBL) Eugon agar, and the term "total anaerobes" includes all organisms culturable on BBL anaerobic agar. Generally these groups of organisms seem to undergo the same changes as do the coliforms. The decreases in numbers of both aerobes and anaerobes during medication were often

‡ References 3, 4, and 8.

much less marked, and in no case were they eliminated completely. Clear-cut exceptions were noted in two subjects (T. S., D. L.) in whom the numbers of coliform organisms decreased while the numbers of total aerobes and total anaerobes showed only slight change.

Periods of from 0 to 17 days following discontinuance of medication were required for the numbers of total aerobes and total anaerobes to return to their predrug levels (Table 3). The average was about seven days.

3. Yeasts: Yeasts were found in 11 subjects. Of 142 representative strains isolated from these 11 subjects, 109 (77%) were considered to be Candida albicans.[15] Only C. albicans was isolated from 6 of the 11 subjects in whom yeasts had been found. The other five subjects had C. albicans and unidentified yeasts.

In most instances the yeasts showed a rapid 100-fold to 1,000-fold increase without undergoing any initial decrease in population during treatment. A period of from 0 to more than 15 days after medication had been discontinued, with an average of 7.5 days, was required for the counts to return to their predrug levels. Four subjects (V. P., M. S., R. P., A. C.), who did not have detectable yeasts before medication, showed the presence and proliferation of yeasts during and following medication. Two subjects (E. B., R. M.) showed fluctuations but no significant increase in the yeast populations during and following treatment. The other nine subjects all showed definite increases in numbers of yeasts in response to medication.

4. Staphylococci: Staphylococci were studied in the feces of 18 subjects. Their responses to medication were, in general, less uniform than those of the other organisms studied. However, three major patterns are illustrated in Figure 2.

In three subjects (H. B., A. B., V. P.) the decrease or disappearance of staphylococci was quickly followed by an increase in the population up to or above predrug levels. There was a complete disappearance of the staphylococci in two of these subjects (H. B., A. B.), whereas the remaining subject (V. P.) showed only a small decrease in numbers of staphylococci during medication.

In three subjects (A. P., K. C., D. L.) there were some fluctuations but no significant changes in staphylococcal populations due to treatment.

A 100-fold to 1,000-fold increase without any initial decrease in population was noted in 12 subjects (67% of cases). Half of these subjects showed maximal increases in staphylococci during medication, and the other half showed maximal increases following discontinuance of medication.

It took a period of from 2 to 15 days, or slightly longer, following cessation of treatment for the number of staphylococci to return to their predrug levels.

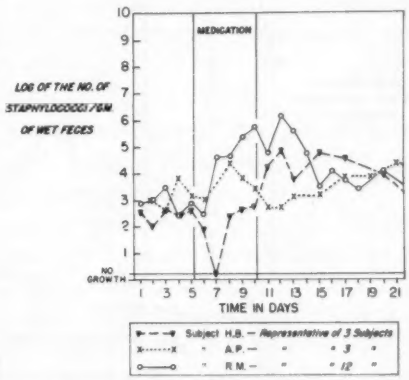
MEDICATION
LOG OF THE NO. OF STAPHYLOCOCCI / GM. OF WET FECES
NO GROWTH
TIME IN DAYS
Subject H.B. — Representative of 3 Subjects
" A.P. — " " 3 "
" R.M. — " " 12 "

Fig. 2.—Patterns of alteration in staphylococci.

Seven subjects harbored Staph. aureus. Two of these subjects did not have this organism until medication. In one case (J. P.) it was found during medication, and in the other (M. C.), after discontinuation of medication. The other five subjects all showed the presence of Staph. aureus during the predrug period. Further study of representative strains isolated from the seven subjects showed that the staphylococci isolated from two subjects (M. S., M. C.) were coagulase-negative and hemolytic, but those isolated from the other five (M. P., J. P., W. L.-II, J. B., K. C.) were coagulase-positive, hemolytic, and mannitol-fermenting.

During medication an interesting shift between Staph. aureus and Staph. albus was noticed in four subjects (M. S., J. B., W. L.-II, K. C.) receiving chlortetracycline and in one subject (M. P.) receiving oxytetracycline. Staph. aureus was totally replaced by Staph. albus. In three subjects (M. P., M. S., W. L.-II) the latter proliferated rapidly towards the end of the medication period, and, with cessation of medication, Staph. aureus reappeared at the time the population of Staph. albus had started to decline. In another subject (J. B.) Staph. aureus did not return for as long as seven days following discontinuance of medication (further fecal samples were not available).

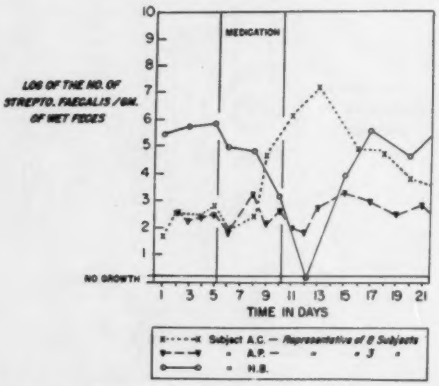
MEDICATION
LOG OF THE NO. OF STREPTO. FAECALIS / GM. OF WET FECES
NO GROWTH
TIME IN DAYS
Subject A.C. — Representative of 8 Subjects
" A.P. — " " 3 "
" N.B.

Fig. 3.—Patterns of alteration in Streptococcus faecalis.

Complications due to staphylococci did not develop in any of the subjects studied.

5. Streptococci: Organisms which grew in Difco Streptococcus faecalis (S F) medium were considered to be streptococci (probably S. faecalis). Representative cultures were confirmed by Gram stain. The changes in numbers of streptococci were followed in 12 subjects who received chlortetracycline (Fig. 3). In eight subjects there was an increase of 100-fold to 10,000-fold in population without an initial decrease during medication. Four of these subjects (A. K., D. L., T. S., J. P.) had a maximal increase during medication, and the other four subjects (A. C., J. B., K. C., A. B.) showed a maximal increase in about two to eight days following discontinuance of medication.

Three subjects (A. P., W. L.-II, M. S.) showed only insignificant fluctuations in the numbers of streptococci throughout the whole course of study.

Streptococci disappeared completely from the feces of one subject (H. B.) shortly following cessation of medication.

It took from 0 to 17 days for the numbers of streptococci to return to their initial predrug levels following cessation of medication. The average was about five days.

6. Proteus: In this study all non-lactose-fermenting colonies having black centers on Salmonella-Shigella (S S) medium were considered tentatively to be Proteus. Representative colonies were isolated, were specifically identified, and in all cases were found to be Proteus mirabilis.[16] This organism was found in 10 of the 19 subjects studied. Nine subjects receiving chlortetracycline, from whom Proteus could not be isolated before medication, showed the presence of Proteus on the second or third days of medication. In a Proteus carrier receiving chlortetracycline, this organism disappeared on the fourth day of medication, followed by a reappearance and a marked rise in numbers to above the initial predrug level. In almost all cases rapid proliferation of this organism to over 10^7 organisms per gram of wet feces occurred within four days following the appearance or reappearance of the organism. It took a period of from 6 to 25 days following cessation of medication for the organism to disappear or to return to its initial predrug level.

7. Pseudomonas Aeruginosa: The stools of one subject receiving chlortetracycline showed the presence of Pseudomonas (identified culturally) on the third day of medication. It increased in numbers to 10^6 organisms per gram of wet feces in two days, then began to decrease, and disappeared five days after cessation of medication. No ill effects from the rapid proliferation of this organism were observed. This organism was not recovered from the stools of any other subjects.

Serological Studies.—Most investigators consider that infection usually results in a rise in the titer of antibodies directed against the infecting agent. In order to determine whether or not the marked increase in numbers of Proteus in the stools of some of the subjects was accompanied by infection, serological studies were conducted. Agglutination tests were carried out on the sera of nine subjects, all of whom showed a marked increase in numbers of fecal Proteus during medication. Sera were collected from each subject before, during, and after treatment. Only two subjects (M. S., T. S.) showed increases in titers, and these were slight. One subject (M. S.) showed a rise in titer from 0 to 1 : 8 on the 10th postdrug day and 12 days following appearance of Proteus in his feces. The titer dropped to 1 : 4 on the 29th postdrug day (15 days after disappearance of Proteus from his feces). This subject showed no clinical evidence of infection with Proteus. Serum from the other subject (T. S.) had a titer of 1 : 4 on the second day following appearance of Proteus in her feces. Unfortunately, a control specimen of serum taken before medication was not available. Three days after the appearance of Proteus in her feces she developed symptoms of Proteus urethritis which lasted for about 10 days. The agglutinin titer of her serum increased to 1 : 16 six days after disappearance of Proteus from her feces but 18 days before disappearance of Proteus from her urine and urethral cultures. Five months after complete recovery the titer dropped to ± in a dilution of 1 : 2. Sera from the remaining seven subjects did not show the presence of detectable antibody at any time.

Complications Following Medication.—In general, the dosages of the drugs used were well tolerated. Rapid proliferation of Proteus, staphylococci, yeasts, Pseudomonas, or other organisms were not associated with diarrhea or disseminated infections in any subjects studied. One female subject (T. S.), however, developed symptoms of urethritis during the time of rapid proliferation of P. mirabilis. The symptoms started four days after chlortetracycline therapy was initiated, three days after the appearance of Proteus in her stool, and almost coincided with the time of maximal increase in fecal Proteus population. P. mirabilis, identical with the Proteus in her feces, was repeatedly isolated and was the predominant organism in the urethral discharge and first portions of her urine specimens. The organism was found to be completely resistant to chlortetracycline but somewhat sensitive to streptomycin on disc-sensitivity test. The symptoms lasted for about 10 days, but the organisms did not disappear from her urine and urethral cultures until the 33d postdrug day (24 days after disappearance of Proteus from her feces). She received 8 gm. of sulfisoxazole (Gantrisin), 1,600,000 units of penicillin, and 2 gm. of dihydrostreptomycin during a two-day period four days after complication had started.

COMMENT

It is evident from the data presented that administration of chlortetracycline or oxytetracyline results in changes of the fecal flora of normal humans varying considerably from subject to subject and from organism to organism. Predictions cannot be made with certainty. Generally speaking, changes in the fecal flora during oral administration of chlortetracycline or oxytetracycline, as detailed here, are less marked than those reported by other investigators. This may, in part, be a reflection of a general trend in the direction of increased antibiotic resistance of the normal flora of humans as a result of the widespread use of antimicrobial agents.§ It is not our intention to give the impression that broad-spectrum antibiotics have no value whatsoever for preoperative use as a means of producing intestinal antisepsis. One should, however, be aware of the possible complications and consequently the limitations in the use of these drugs. With the dosage used during this investigation the maximum effect of the antibiotics might be expected only during the first two to three days of medication, and adverse effects beyond that time.

§ References 18, 19, and 28.

The increase in numbers of coliform, total aerobe, and total anaerobe organisms during medication, with or without an initial decrease in numbers, found in this study agrees well with some of the findings of Ganey and co-workers,[9] Morton and co-workers,[13] and Allen.[12] However, more detailed data have been obtained in the present investigation. The replacement of Escherichia coli by Klebsiella (Aerobacter aerogenes) during medication, as found in two (A. P., K. C.) of the four subjects of this series (unpublished work), may be a factor in the secondary increase of the coliform organisms. The persistence of Klebsiella during medication has been observed by Sborov and associates[20] in patients during treatment with chlortetracycline. The increase in numbers of coliform organisms is usually reflected in a similar increase in total aerobes and anaerobes (including facultatives), of which the coliform organisms form a major portion. Exception to this is quite evident in at least one subject (T. S.), whose coliform organisms showed a decrease toward the end of the medication period while the numbers of her total aerobe and total anaerobe organisms showed increases due to rapid proliferation of Proteus to above the coliform population.

The increase of staphylococci, yeasts, streptococci, and Pseudomonas as reported here is in agreement with practically all the recent reports in the literature concerning the effects of these two antibiotics.

The growth of yeasts seems to be stimulated by the medication in a great majority of the cases, either directly || or indirectly through suppression of other organisms. The incidence of C. albicans in feces as found here appears to be higher than previously reported.¶

The incidence of Proteus in feces increased from about 5% before medication to about 50% following medication. The former figure is still comparable to the 10% incidence found by Rustigian and Stuart,[25] who used direct plating of fecal specimens. Of all the micro-organisms studied during this investigation, Proteus seemed to react most profoundly to the medication with a rapid and marked increase in population. These organisms did not disappear or return to their initial predrug level until from 6 to 25 days after the cessation of the medication. Despite the changes noted in 10 of the 19 subjects studied, no evidence whatsoever has been obtained to suggest that a marked increase in numbers of Proteus might be responsible for a dysentery-like diarrhea.

The overgrowth of Proteus seemed to exert varying degrees of suppression on coliform organisms in two subjects (A. B., T. S.), on staphylococci in three subjects (T. S., A. P., W. T.), and on streptococci in two subjects (W. L.-H, A. B.). These organisms showed an actual decrease or at least a suspension of their original tendency to increase while Proteus flourished. They tended to return to their original numbers after Proteus had started to decline. Whether or not this is a matter of specific microbial antagonism or only the result of simple suppression due to overgrowth of one organism remains to be investigated.

The increases in agglutinin titers in the sera of two subjects (M. S., T. S.) indicate the presence of Proteus infection. Infection, if any, in M. S. was subclinical in nature, whereas the urethritis in T. S. was clinically obvious. In the remaining seven Proteus-carrying subjects studied serologically, the failure to develop antibodies as demonstrated by agglutination tests may be, in part, due to the failure of Proteus to invade the host tissues, resulting in insufficient antigenic stimulation.

There are many reports in the literature which are in disagreement with the data presented here concerning changes in the fecal flora of man. Several factors may be responsible for these differences of opinion. Some of these are as follows:

1. Difference in dosage of the antimicrobial agents used. McVay[8] has clearly demonstrated that larger doses can produce greater suppression of the intestinal flora than the smaller doses of the same antibiotic under the same experimental condition.

|| References 21 and 22.

¶ References 23 and 24.

2. Difference in level of the intestinal tract where the micro-organisms were isolated. Again, in McVay's investigation,[8] comparing the effects of chlortetracycline (Aureomycin) on fecal flora and on intestinal flora isolated through cecostomy and colostomy wounds, it is evident that organisms comprising the intestinal flora from higher levels were suppressed earlier and to a greater extent than those present in feces. This view is supported by the findings of Johansson and co-workers.[26]

3. The use of adjuvant preoperative measures such as colonic irrigation, catharsis, and low-residue diet to reduce the population of intestinal flora.

4. Difference in techniques of counting. We are in entire agreement with Metzger and associates,[27] who have expressed the opinion that discrepant results may be obtained with a simplified streak plate technique as compared with the serial dilution-pour plate technique. It is also our experience that by using techniques and media different from those of Dr. T. M. Gocke, of the Boston City Hospital, for daily study of the same fecal suspensions (10^{-1} dilution), from the same test tubes, the results obtained were different from those of Dr. Gocke. Nevertheless, the general trends obtained by the two groups of investigators agree fairly well for a majority of the organisms studied.

5. Differences in response of the host as clinically observed, in degrees of sensitivity of the intestinal flora to antibiotics, and in the microbial environment. As Morton and associates [13] have clearly pointed out, bacteriological evidence does not always confirm the clinical results. The degree of sensitivity not only is an inherent characteristic of the intestinal flora itself but may also be modified by previous medication. With regard to the microbial environment, any factors, such as psychic phenomena, side-reactions of the drug itself, concomitant infection causing intestinal spasm or distension, etc., capable of altering the environment in the intestinal tract, might complicate interpretations of alterations of the fecal flora.

SUMMARY

Alterations in the fecal flora of 19 normal subjects who received either chlortetracycline or oxytetracycline are described.

Generally, the changes in the fecal flora as a result of medication vary considerably from subject to subject as well as from organism to organism. In the majority of cases, the coliform, total aerobe, and total anaerobe organisms behave in a similar fashion—a decrease followed by a secondary rise in population during medication. Yeasts and Proteus generally increased during medication. Proteus seemed to undergo the most marked and persistent alteration. Staphylococci and streptococci responded to medication in a less predictable manner.

Oral administration of these antibiotics does not render the intestinal tract sterile and may, in fact, only reduce the population of organisms in the lower intestine for a short period of time.

No evidence was obtained that a marked proliferation of Proteus causes a dysentery-like diarrhea. The only significant complication following medication noted in this investigation was the development of Proteus urethritis in one female subject.

There was an increase in antibody against Proteus in only two of nine subjects in whom Proteus proliferated.

Some important factors contributing to the conflicting reports in the literature on the effect of these antimicrobial agents are discussed.

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PROBENECID (BENEMID)

Its Uses and Side-Effects in 2,502 Patients

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PROBENECID (Benemid) * resulted from a prolonged research effort directed toward the discovery of a safe agent that, administered orally, would physiologically inhibit the renal tubular secretion of penicillin.[1] Introduced into clinical medicine on July 22, 1949,[2] the use for which it was intended has increased steadily, and new indications for the drug have been disclosed. A conservative estimate indicates that 4,000,000 patient days (15,626 patient years) of therapy have been administered. Granting that the record of side-effects following the use of any therapeutic agent is not static, and that continuing use will bring to light an increasing number of side-effects and toxic manifestations, an appraisal from time to time seems appropriate. A preliminary assessment of the toxicity of probenecid was presented in 1951 on the basis of 701 patients,[49] and it is now possible to report on 2,502 patients. The information reported here has been derived from published articles, from the reports (unpublished) of many investigators who have communicated with the authors, and, lastly, from a large series of patients treated by the authors.

USES OF PROBENECID

Probenecid was developed for the specific purpose of inhibiting the renal tubular secretion of penicillin. The penicillemia resulting from any given dose of penicillin, regardless of the route of administration or the type of penicillin administered, is enhanced 2 to 10 times.† Probenecid is used in combination with orally administered penicillin, and also in conjunction with large doses of parenterally administered penicillin, for the treatment of so-called "resistant" infections, very particularly subacute bacterial endocarditis.‡ Of academic interest has been the occasional success of massive penicillin therapy enhanced by probenecid in the treatment of typhoid infections.§

Originally proposed as an adjuvant to penicillin therapy, it was promptly discovered that, predicated upon previous experiences with carinamide,[13] probenecid has a profound uricosuric effect.[14] It seems reasonably clear that (*a*) probenecid inhibits the tubular reabsorption of uric acid || in gouty patients and lowers elevated serum uric acid levels to normal or high normal values,¶ (*b*) that the uric acid excreted into the urine by gouty persons can be tremendously increased,# (*c*) that the turnover rate of the miscible pool of uric acid in gouty patients can be favorably influenced,* and (*d*) that tophi can be prevented and destructive lesions in the bone actually made to heal.† Probenecid has been established as an outstanding contribution to the management of chronic gout and gouty arthritis.

Probenecid administered together with *p*-aminosalicylic acid (PAS) results in enhancement by 15 to 50% of the plasma concentrations of PAS. Although this increase in plasma concentrations of PAS is not of the same magnitude as that observed with penicillin, it is nevertheless reflected in terms of increased tuberculostatic activity of human

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* Benemid is the trademark of Merck & Company, Inc., for *p*-(dipropylsulfamyl) benzoic acid.

† References 2-5.

‡ References 6-9.

§ References 10-12.

|| References 15-18.

¶ References 20-22.

References 23 and 24 and Talbott, J. H., and Lockie, L. M.: Personal communication to the authors.

* References 25-27.

† References 28-30 and 57.

plasma.[31] The original observations [34] have been confirmed,‡ but not uniformly.§ It is doubtful whether it is possible in man to correlate therapeutic effectiveness with the circulating plasma concentrations of PAS and to quantitate benefits of probenecid effects on PAS. However, the therapeutic implications of PAS enhancement by probenecid are clear in carefully controlled animal studies.[39]

Probenecid apparently inhibits the reabsorption of phosphate by the renal tubules, with consequent influence upon the plasma concentrations of phosphate and calcium. Familial nephrogenic osteopathy is uncommon, but the favorable influence of probenecid upon this disease and the ease of handling of the hyperphosphatemia of these patients is noteworthy.[40] The interrelationship of plasma, calcium, and phosphorus is well known, and in familial nephrogenic osteopathy with elevated phosphates it was observed that probenecid caused a lowering of the phosphate level and a slight elevation of calcium. Similarly, it has been observed that the tetany of hypoparathyroidism can be controlled with probenecid.‖ Whether probenecid will prove to be a contribution to the therapy of this condition must await further evaluation.

Perhaps of only academic interest has been the demonstration that probenecid has an enhancement effect upon the plasma concentrations of pantothenic acid when it is administered either orally or parenterally.[42]

Probenecid has a slight, but probably clinically insignificant, enhancement effect upon the plasma concentration of sulfapyrimidines.[43] Probenecid does not increase the plasma concentrations of streptomycin, chlortetracycline, oxytetracycline, chloramphenicol,[44] or neomycin.¶ The most recently claimed pharmacologic effect of probenecid has been its influence upon sodium and water excretion in cardiac patients.[55] In normal animals and humans these effects have not been observed.#

ADMINISTRATION OF PROBENECID

By preference, probenecid is administered orally. The drug is rapidly absorbed from the gastrointestinal tract, so that measurable concentrations are observed in the plasma within a half-hour after the administration of as little as 0.5 gm.[6] Because probenecid is eliminated by glomerular filtration alone, significant plasma concentrations of the drug are observed for as long as 24 hours following the administration of a single 1 gm. dose.[6] It has been suggested that probenecid is almost completely reabsorbed by the renal tubules and is slowly degraded within the body.[1] An average patient with normal renal physiology ingesting a dose of 2 gm. per day, administered either as 1 gm. every 12 hours or as 0.5 gm. every 6 hours, will show continuing plasma concentrations in the range of 4 mg. per 100 ml.[6] In animals * and in man [6] this concentration of probenecid results in full pharmacologic effects.[46]

Greater enhancement effects in proportion to the increased doses, from 0.5 to 4 gm., can be demonstrated.† Nevertheless, experience has shown that 2 gm. per day represents the average dose which is tolerated, and when this dose is exceeded the plasma concentrations of probenecid may gradually increase to the point of intoxication. A limited experience has indicated the likelihood that plasma concentrations in excess of 30 mg. per 100 ml. will produce central nausea and vomiting.‡ Accordingly, the daily dose of 2 gm. has been set, not as the optimal dose but rather as that dose which will be tolerated by the average patient over prolonged periods of time. Indeed, in those patients with compromised renal function,

‡ References 32, 33, and 36.

§ References 35, 37, and 38.

‖ Hoffman, W. S.: Personal communication to the authors, and Reference 41.

¶ Boger, W. P.: Unpublished data.

Boger, W. P.: Unpublished data.

* References 1 and 45.

† References 4 and 47.

‡ Boger, W. P.: Unpublished data.

2 gm. a day is excessive, and if probenecid effects are desired the dose must be decreased by trial and error to that point at which symptoms are not observed.

When employed in the therapy of gout, probenecid is used in daily doses varying between 0.5 and 2 gm. per day. There is no fixed optimal daily dose, and authorities of comparable experience indicate their preference for the use of 0.5, 1, 2, and even more grams per day under specific circumstances. Responses in terms of serum uric acid and uric acid elimination in the urine vary from patient to patient, as little as 0.25 and 0.5 gm. per day resulting in profound lowering of the serum uric acid level and outpouring of urates into the urine, whereas in other patients 2 gm. and, in some exceptional situations, even 3 and 4 gm. per day § are required to achieve the same effects. These seeming discrepancies can probably be explained on the basis of differences in renal function.||

Although probenecid is used primarily by the oral route, the sodium salt can be administered intravenously. There are few indications for administering the drug intravenously. During certain renal function investigations, it has been found that 2 and even 4 gm. of probenecid could be safely administered intravenously.

Probenecid has been used most extensively in the therapy of chronic gout and combined with orally administered penicillin. Patients treated for acute infections have received probenecid over limited periods of time, 3 to 10 days, whereas patients with chronic gout have ingested probenecid continuously for periods as long as four years.¶ In conjunction with penicillin, probenecid has been administered to patients suffering from a wide variety of disease conditions. Probenecid is administered either for short periods in connection with the handling of acute infections or for prolonged periods in the treatment of subacute bacterial endocarditis, gout, or pulmonary tuberculosis. The doses and the periods over which these doses have been administered are indicated in Table 1. The administration of any drug over periods of years is a rigorous test of safety, to which few therapeutic agents are put, and under these circumstances probenecid has established itself as a drug of low toxicity.

§ Bartels, E. C.: Personal communication to the authors.

|| References 24, 28, and 57.

¶ Reference 22 and Talbott, J. H., and Lockie, L. M.: Personal communication to the authors.

SIDE-EFFECTS OF PROBENECID

In Table 2 are presented the side-effects that have been observed, and they are tabulated in terms of numerical incidence and percentage occurrence. Severe side-effects have been rare, the most serious being those of hypersensitivity, with the development of chills, fever, rash, myalgia, shortness of breath, nausea, vomiting, and vasomotor collapse. At the present writing, there have been no fatalities attributable to probenecid. Eight unmistakable cases of hypersensitivity have been reported.# Three of these cases are described in some detail.

TABLE 1.—*Dosage and Duration of Probenecid Administration in 2,502 Patients*

Dose, Gm./Day	Duration	Patients, No.
Intravenous administration		
1	Single dose	7
2	Single dose	29
3	Single dose	10
Oral administration		
Up to 1	1-14 days	95
	2-4 wk.	10
	4-8 wk.	11
	8-12 wk.	2
	3-6 mo.	8
1-2	Single dose	269
	1-14 days	1,282
	2-4 wk.	119
	4-8 wk.	58
	8-12 wk.	91
	3-6 mo.	160
	6-12 mo.	162
	1-4 yr.	98
3-4	1-14 days	49
	2-4 wk.	6
	4-8 wk.	2
	8-12 wk.	2
	3-6 mo.	32
		2,502

References 48 and 53; Austrian, C. R.: Personal communication to the authors; Ragen, C.: Personal communication to the authors.

CASE 1.—A 46 year-old man with chronic gout was being given 2 gm. of probenecid per day. On the 10th day of administration the patient developed headache, generalized muscular aching, itching, shortness of breath, nausea, vomiting, a shaking chill, and a temperature of 103 F.

The continuance of the drug for an additional 24 hours resulted in the development of a macular rash that covered the body. The symptoms subsided rather promptly upon discontinuing the drug, and the suspicion was strong that probenecid was the cause of the foregoing symptoms. Two weeks subsequently, probenecid was administered again, in a dose of 0.25 gm., and within the hour the initial symptoms recurred.

TABLE 2.—*Toxic Side-Effects of Probenecid in 2,502 Patients**

	Numerical Incidence	Percentage of Incidence
Gastrointestinal symptoms	78	3.1
Anorexia	2	
Nausea	25	
Vomiting	6	
Diarrhea	1	
Gastrointestinal upset	40	
Abdominal discomfort	2	
Gaseous burning	2	
Hypersensitivity reaction	8	0.31
Drug fever	9	0.36
Skin rash	34	1.35
Renal colic or passage of urate stones	17†	0.68
Costovertebral pain	2†	0.08
Hematuria	2†	0.08
Precipitation of acute gout	31	1.20
Flushing	1	0.04
Headache	Seen occasionally	
Reducing substance in urine	14	0.55
Dizziness	1	0.04
Anemia	1	0.04
NPN elevation	3	0.12
	201	7.94

* Probenecid was coadministered with penicillin in the great majority of patients in this review, and sensitivity to penicillin itself probably exceeds the sensitivity to probenecid.

† These symptoms are almost certainly due to concretions or urates which have been excreted into the urine in excessive amount as a direct result of the pharmacologic action of probenecid, for which it was administered. A reasonable question can, therefore, be raised as to whether these symptoms should be considered "toxic" effects.

CASE 2.—A 65 year-old man received 2 gm. a day for 10 days, and thereafter, 1 gm. for an additional 20 days, without reaction. Approximately 10 months later this patient received a single dose of 0.5 gm., and within 30 minutes there was marked itching of the feet and hives, with swelling of the face and scalp. Shortly thereafter the patient developed sweating, weakness, faintness, pallor, and tachycardia and showed a declining blood pressure. These signs subsided gradually during the night, and the patient recovered. Several months later, a small quantity of drug (scraped from a tablet) was administered orally, and a mild reaction ensued.

CASE 3.—Allergic phenomena became manifest following the administration of probenecid in a dose of 1 gm. daily for a period of four weeks. The chills, fever, and elevated sedimentation rate subsided promptly upon withdrawal of the drug.

Additional cases of drug sensitivity may have been observed, but these have not come to our attention. The arbitrary criterion can be established that no case of drug sensitivity can be accepted beyond cavil unless the patient is challenged with the offending medication some time after recovery from the original symptoms of sensitization. Such a critical attitude is unwarranted, for some patients are so exquisitely sensitive that exposure to the drug may threaten life. The satisfaction of establishing an academic point does not, in our minds, warrant the acceptance of such risks, and if reasonable suspicion exists that a patient has become sensitized to a given agent it is better that this agent be discontinued and not employed subsequently unless anticipated benefits far outweigh the risks. Probenecid has been administered intermittently to some gouty patients, and it is in such patients that drug sensitization is most likely to occur. Once the decision has been reached to employ probenecid, the therapy should be continued indefinitely.

Skin Rash.—The skin rashes have been described as being scarlatiniform, diffuse maculopapular, urticarial, or merely as "allergic" and were usually accompanied by fever. In at least five of these patients probenecid was being administered in conjunction with penicillin, and the frequency of rashes as a result of penicillin therapy alone is well known. For purposes of this report, there was no distinction made between probenecid and penicillin as potential causes of the rash, and the rash has been accepted as an untoward effect of probenecid administration.

Drug Fever.—Fever apart from rash has been noted in nine patients. The development of fever is properly considered as a manifestation of drug sensitivity.

Headache.—Headache has been observed "occasionally," and it has not been possible to assign the specific causative role of probenecid. Apart from the symptom complex of drug sensitivity, headache has in no case been severe enough to necessitate discontinuance of therapy.

Gastrointestinal Symptoms.—These symptoms have varied in character and intensity from vague abdominal distress to anorexia, nausea, vomiting, and abdominal cramps and from epigastric burning to frank vomiting and diarrhea. In the majority of instances the symptoms have been mild and have not necessitated cessation of therapy. The administration of the daily dose in smaller subdivisions or care in administering the doses of probenecid along with food have frequently alleviated the symptoms. Symptoms have been correlated with the size of the dose in 91 patients who received 3 gm. of probenecid per day and who noted gastrointestinal complaints. The side-effects in almost all these patients were lessened when the dose was decreased to 2 gm. or less per day. Three grams per day is an unnecessarily large dose for the majority of patients, and there are relatively few justifications for administering more than 2 gm. per day for longer than a few days.

The mildness of the gastrointestinal symptoms may be judged from the experience of one investigator.* who indicated that 15 of 84 patients receiving between 0.5 and 2 gm. per day developed some gastrointestinal symptoms but that in only 2 were symptoms severe enough to require temporary cessation of therapy.

Of the 78 patients in the entire series in whom gastrointestinal symptoms were noted, it was necessary to discontinue therapy in only 8. In the majority of patients the symptoms were sharply reduced or eliminated by lessening the daily dose of drug.

Side-Effects Referable to the Uricosuric Effects of Probenecid.—Other observers † have drawn attention to the possibility of the development of urate gravel and crystalluria, although they, themselves, saw such side-effects in only two patients. Hematuria presumably due to the irritation or trauma of urates that had crystallized in the urinary tract has been reported in two patients.[21] Microscopic hematuria has been observed.[49] The costovertebral pain observed in two patients is almost certainly assignable to the deposition of urate crystals in the renal pelves and must be accepted as an effect due to the pharmacologic action of probenecid. Thirteen of 84 patients receiving probenecid for treatment of gout complained of renal colic or passed urate gravel.‡ In four of these patients the drug had to be discontinued.

It is a question whether these manifestations of urate gravel in the urine, costovertebral pain, renal colic, and hematuria, gross or microscopic, should properly be regarded as toxicity of probenecid. Probenecid is administered to the patient with gout because urate excretion can be greatly increased over control values by the administration of probenecid § and there is the hope of depleting the miscible pool of uric acid and preventing the laying down of tophi. The insolubility of uric acid in water and in urine is well known; hence there is no gainsaying that if the solubility of uric acid in water is exceeded there will be a settling out of urate crystals. For the reason that probenecid increases the outpouring of uric acid in the urine, it contributes to the precipitation of urate crystals in the urinary tract. Whether this should be called "drug toxicity" can be debated.

This complication can be avoided by scrupulous alkalinization of the urine during probenecid therapy. Alkalinization is particularly recommended during the first weeks of probenecid therapy, when excessive quantities of uric acid are withdrawn from the miscible uric acid pool and excreted into the urine.

Another approach to the prevention of uric acid concretions in the urinary tract is

* Gutman, A. B.: Personal communication to the authors.

† References 21 and 24.

‡ Gutman, A. B.: Personal communication to the authors.

§ References 14-16.

the initiation of probenecid therapy with small oral doses, i. e., a single 0.5 gm. dose per day or 0.25 gm. twice a day for the first week of treatment and 1 gm. per day thereafter. Only after it has been demonstrated that 1 gm. per day is insufficient to produce marked lowering of serum uric acid is it deemed advisable to administer as much as 1.5 or 2 gm. per day.

A reducing substance in the urine has been reported in 14 patients who have received probenecid. This is probably due to the presence of a glucuronic acid conjugate of probenecid, although this point has not been established. This surmise seems justified on the basis of previous demonstrations that carinamide (the forerunner of probenecid) causes a reducing substance to appear in the urine that has been identified as a glucuronide conjugate.

PRECIPITATION OF ACUTE ATTACKS OF GOUT

The causal role of probenecid in the precipitation of gouty attacks is not clear, but it has been reported in 41 patients. There is no sure way of distinguishing between those attacks which might have occurred spontaneously and those that occurred in close temporal relationship to the initiation of probenecid therapy. Investigators of considerable experience || entertain strong feelings that probenecid can precipitate acute attacks during the early weeks of therapy. Probenecid can contribute to the precipitation of acute attacks.[57] One of us (W. P. B.) has observed a gouty patient who had an acute attack of gout within one week after the initial administration of 0.5 gm. of probenecid; the condition was quiescent during three weeks of such therapy, and then, within three days after the increasing of the daily dose to 1 gm. a day, there was a severe attack, which required full colchicine therapy. The dose of 1 gm. per day was continued for five weeks, and then, within a week after the increasing of the daily dose to 2 gm. a day, the patient had another severe attack. This patient was so thoroughly discouraged that therapy was discontinued entirely, and, indeed, the patient absented himself from the clinic for a period of four months. Upon his return and specific request that therapy be reinstituted, a daily dose of 0.5 gm. was administered, and, again, within the week he had a severe attack. Therapy was continued, and the symptoms of the acute attack were handled with colchicine, and with a modest dose of 0.5 gm. per day for an extended period of time his disease has been brought under control.

Although the natural course of gout is highly variable and persons of the greatest experience are the most reluctant to draw conclusions, the impression nevertheless exists that with continuance of probenecid therapy the frequency and severity of acute gouty attacks lessens. Before final judgments can be made, extensive study over a period of years is obviously needed.

TOXICITY

Chronic Toxicity.—Probenecid has been aptly described as the "insulin of gout,"¶ and there are those who believe that once the diagnosis of gout has been established without question, and the patient has suffered a number of typical attacks, probenecid therapy is amply justified as a prophylactic against the development of future complications of gout. It has been suggested that the younger the patient, the more desirable it is for probenecid therapy to be instituted. Regardless of the attitude which may be taken upon this matter, the fact remains that patients suffering from gout have now received probenecid continuously for periods up to four years, and an increasing number of patients have received the drug continuously for a year or longer. It is still too early to make final judgments about the eventual safety and lack of toxicity of probenecid, but at the present writing one can say that it has shown a surprising lack of toxicity in those patients who have received it for the most prolonged periods.

|| References 15 and 20 and Bartels, E. C.: Personal communication to the authors.

¶ Bartels, E. C.: Personal communication to the authors.

Hemopoietic Toxicity.—A single patient has been reported who developed moderate anemia during the fourth week of probenecid therapy,[51] and this case has been previously reported. To date there have been no cases of agranulocytosis reported, none of purpura, and, once again, patients who have received the drug for years have failed to show any abnormality of the hemogram.

Renal Toxicity.—The reversible and physiologic inhibition of renal tubular functions invokes the question of potential renal toxicity. It is well known that the impairment of renal function is common in gouty patients.# Eleven to 23% of these patients are reported to develop uric acid stones.[58] Notwithstanding, probenecid has been administered to such gouty patients and has shown its usual beneficial effects without evidence of aggravation of already existent renal impairment. The suggestion is actually made that, by its drawing upon the miscible uric acid pool, the deposits of urate crystals in the parenchyma of the kidney, or in the renal tubules, may be lessened and thus the function of the kidneys improved.

Probenecid has actually been administered to two patients with already elevated nonprotein nitrogen (NPN) estimations, and no increase in the NPN was noted. Well-controlled studies [52] on the metabolic and renal effects of probenecid have demonstrated no effect on nitrogenous products or on oxygen consumption by the kidney.[60] Renal function tests have demonstrated the inhibition of phenolsulfonphthalein excretion and the prompt reversibility of this inhibition when probenecid has been discontinued.[46] Measurement of renal functions in terms of creatinine, mannitol, and *p*-aminohippurate (PAH) clearances has demonstrated no adverse effect by probenecid upon renal function.[46] Those few patients who have died as a result of infectious disease under treatment with penicillin and probenecid have failed to show any evidence of damage to the kidneys that might be assignable to drug toxicity.

References 58 and 59.

Hepatic Toxicity.—No hepatotoxicity has as yet been reported.[27] Liver-function tests performed after (more than) three years of continuous therapy with probenecid have failed to show any evidence of compromising of these functions.[22]

COMMENT

The periods of time over which probenecid has been administered to patients have been dependent upon the indication for which it was administered. In the therapy of chronic gout the drug has been given continuously for years, and if one assumes that gout is a genetic fault of the metabolism, leading to constant overproduction of uric acid, the need for the corrective influences of a uricosuric agent such as probenecid continues as long as life lasts. With *p*-aminosalicylic acid in the treatment of tuberculous patients the administration of probenecid is less prolonged, but the duration of therapy is measured in months and perhaps in years. It is in the treatment of gouty and tuberculous patients that the largest experience, with regard to chronic toxicity of probenecid, has been obtained. In these groups of patients the drug has proved itself to be singularly safe, and the side-effects have been overshadowed by the benefits accruing.

Originally developed as an agent capable of enhancing the penicillemia resulting from the administration of penicillin by any route, probenecid administered for this purpose is seldom prescribed for longer than a week. Virtually no toxicity has been observed as a result of short-term administration of the compound.

The most significant side-effects resulting from the administration of probenecid, regardless of the time over which it is administered, have been gastrointestinal symptoms. In the main, these symptoms can be correlated either with the size of the daily dose or with the resulting plasma concentrations of probenecid. When plasma concentrations exceed 30 mg. per 100 ml., it is not uncommon to observe nausea and gastrointestinal distress.[46] The plasma concentrations of

probenecid can be closely correlated with renal function, since the drug is eliminated almost entirely by glomerular filtration rate and, consequently, its elimination from the body is exceedingly slow. Any glomerular dysfunction may, therefore, contribute to accumulation of the drug in the circulation. Gastrointestinal symptoms are usually controlled by lessening the daily dose, and this, in turn, accomplishes a lowering of probenecid concentration in the plasma.

SUMMARY

A review of 2,502 patients indicates that probenecid in a daily dose of 2 gm. can be safely administered for periods up to four years. The most common manifestation of intolerance is gastrointestinal symptoms, occurring in 3.1% of patients studied. Typical hypersensitivity reactions have been observed in 8 patients, and skin rashes have been observed in 34 patients. The rashes observed have not always been attributed with certainty to probenecid, and the likelihood exists that some of them were due to concurrently administered penicillin.

There is reasonable presumption that probenecid, by reason of its profound uricosuric action, may in some cases act as a chemical stress upon the biochemical equilibrium of the gouty patient and precipitate an acute gouty attack. Tentatively, the statement is made that approximately 10% of gouty patients treated will suffer an acute attack of gout shortly after the institution of probenecid therapy; however, continued probenecid therapy appears to lessen the frequency and severity of acute gouty attacks. Apart from the influence on gouty attacks, probenecid-treated patients almost universally attest to a sense of well-being. The laying down of new tophi can be prevented, and uric acid deposits already established may be diminished in size or actually made to disappear.

To date, no deaths are attributable to probenecid therapy. There is no evidence of aggravation of preexistent renal damage; no hepatic toxicity has been observed, and there has been no reported case of suppression of the hemopoietic system. A total of 175 side-effects have been noted in a group of 2,502 patients, representing an over-all percentage of 7.94%. Thirty-five of these reported side-effects were related to the urinary tract, where the question may be raised whether the manifestations are truly side-effects and evidences of toxicity or are, in fact, evidences of the uricosuric activity of probenecid. Probenecid is a drug of low toxicity, an outstanding contribution to the therapy of chronic gout and gouty arthritis and a valuable adjunct to penicillin therapy, orally or parenterally administered.

The authors freely acknowledge their indebtedness to the many correspondents who have made their personal observations available for purposes of this review. In the spirit of honest inquiry and in the hope of being fully advised with regard to the occurrence of side-effects due to probenecid therapy, the authors invite correspondence from the readers of this article and from those who have had experience with probenecid.

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DECREASED RED CELL SURVIVAL ASSOCIATED WITH LIVER DISEASE

Use of Radioactive Sodium Chromate in Measurement of Red Cell Survival

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IT HAS been known for many years that anemia is frequently present in chronic liver disease, especially in cirrhosis of the liver. The etiology, however, has been obscure and has been the subject of considerable discussion. Since the anemia is often macrocytic in type, as first noted by Gram, in 1883,[1] and subsequently confirmed by others,* it was only natural that a deficiency in the anti-pernicious-anemia factor be suspected. This explanation, however, has been largely discredited because of the lack of response to liver extract † and because the bone marrow is rarely megaloblastic in character.‡ In addition, it has been shown by Schiff and coworkers [15] that extracts made from cirrhotic livers are able to produce a hematological remission in patients with pernicious anemia.

In 1904 Bleichroeder first described the occurrence of red bone marrow in the femur of patients with cirrhosis and made the statement that "in cases of cirrhosis of the liver numerous erythrocytes are destroyed in the spleen." [16] Eppinger, in 1920, reviewed the subject and added additional evidence that in some cases of chronic liver disease there is an increased destruction of erythrocytes.[17] However, it was not until 1937 that a large group of patients with liver disease were studied with a method which would detect increased destruction of red cells. In that year Watson reported 7 cases of hemolytic anemia associated with cirrhosis of the liver out of a group of 135 patients with jaundice or hepatic disease.[18] The diagnosis was based primarily on a marked increase in fecal urobilinogen. However, it was thought that such a hemolytic process must be relatively uncommon, since in most cases of cirrhosis the fecal urobilinogen was within normal limits. Subsequently, there have been a few similar cases reported by others.§ Recently, Chapman and Mollison, using the Ashby technique, measured the red cell survival time in five cases of severe decompensated cirrhosis.[23] They found that the survival time was definitely reduced in all five cases. Further suggestive evidence of a hemolytic process in cirrhosis of the liver is provided by the usual finding of some degree of erythroid hyperplasia in the bone marrow ‖ and the frequent occurrence of reticulocytosis in the peripheral blood.[5] The leucopenia and thrombocytopenia which are commonly present ¶ may be associated with increased hemolysis in the syndrome of hypersplenism. Finally, it should be pointed out that hemolytic anemia is sometimes macrocytic in character.

From the above review it can be concluded that a hemolytic process may occur in association with liver disease which is of sufficient severity to produce anemia. It is clear, however, that the problem has been approached from the point of view of the anemia and that little attention has been paid to the significance of increased hemolysis in

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* References 2-10.

† References 4, 5, 11, and 12.

‡ References 10-14.

§ References 19-22.

‖ References 10-14.

¶ References 10, 14, and 24-26.

its relation to the liver disease. No attempt has been made, with the exception of the study by Chapman and Mollison, to determine the incidence and severity of an abnormal hemolytic process in cases of liver disease irrespective of the presence of anemia. Since an increased rate of red cell destruction has important implications relative to liver disease other than that of anemia, it appeared desirable to conduct such a systematic study.

At the present time probably the most accurate way of measuring the degree of hemolysis is to determine the red cell survival time. Until recently techniques satisfactory for our purpose were not available. The Ashby agglutination method, which has been used for many years, is limited to patients with certain blood types, and one does not measure the survival of a patient's cells in his own circulation.[27] In addition, there is a definite risk of transmitting viral hepatitis, a serious consideration in the presence of already damaged livers. Methods utilizing various radioactive and stable isotopes, such as N^{15}, Fe^{59}, and C^{14} are more versatile than the Ashby method, since either genotype-specific or Group O donors can be used,[28] but they all have distinct disadvantages. The N^{15} method requires a mass spectrometer, which is not available in most institutions; C^{14} has a long half life, and Fe^{59} data are difficult to interpret because of reutilization of the iron. Recently, Necheles, Weinstein, and LeRoy # have shown that radioactive sodium chromate can be satisfactorily employed to measure red cell survival time. The validity of the method has been subsequently confirmed by others.* The development of this technique, which fulfills the requirements of our particular problem, has provided us with an opportunity to measure red cell survival times in a series of cases with liver disease. The following report concerns such a study in a series of 19 unselected cases of acute and chronic liver disease. A preliminary report has been presented elsewhere.[33]

References 29 and 30.

* References 31 and 32.

METHODS AND MATERIAL

Nineteen patients with various types of liver disease were studied (Table 1). Only cases with clear-cut objective evidence of liver disease who were able and willing to cooperate were included. Otherwise they were unselected and chosen entirely at random. Fifteen had cirrhosis of the liver. Of these there were nine (E. F., V. S., R. P., S. I., J. D., N. F., G. K., E. K., and M. G.) who gave a definite history of excessive alcoholic intake and could probably be classified as having "alcoholic" or "Laennec's" cirrhosis; one (J. S.) had definite hepatitis following yellow fever vaccine in 1942 and also had arsenic therapy in 1945 for syphilis; four (J. C., T. Z., B. C., and B. M.) had a history of probable antecedent hepatitis and, in addition, one (B. M.) also gave a history of arsenic therapy; one (A. C.) had xanthomatous biliary cirrhosis.

Of the remaining four cases, two had chronic hepatitis; one patient (S. G.) developed jaundice in 1942 upon receiving yellow fever vaccine and, three years later, in Italy, had acute hepatitis; the other (W. G.) had hepatitis following a whole blood transfusion and had also used potassium arsenite (Fowler's) solution for psoriasis over many years. There was one patient (H. C.) who had chronic biliary obstruction secondary to cholecystectomy. This obstruction had been relieved before the period of the present study, although biopsy at the time of surgery showed a moderate increase in fibrous tissue of the liver. The last patient (E. M.) had a typical acute viral hepatitis and was studied during the acute phase of his illness.

General data regarding these patients is shown in Table 1. It is obvious that there was much variation in severity and in the manifestations of the disease process as well as in the responsible etiologic factors. Liver biopsies, either by surgical exploration or by use of a biopsy needle, were obtained in all cases except in the patient with acute hepatitis and three of the patients with cirrhosis. Biopsy was not done in these last three cases because of the presence of a bleeding tendency. In these four patients the diagnosis was confirmed by typical clinical and laboratory findings, including evidence of portal hypertension in those with cirrhosis.

The red cell survival time was studied with radioactive sodium chromate ($NaCr^{51}O_4$),† using the subject's own blood. This method has been reported in detail elsewhere.[29] Standard hematologic procedures were used to measure the hematocrit and

† The radioactive sodium chromate used in these studies was obtained from the Abbott Laboratories on allocation from the Isotopes Division, United States Atomic Energy Commission, Oak Ridge, Tenn.

TABLE 1.—*Clinical Data*

Patient	Age	Sex	Diagnosis	Duration of Symptoms, Yr.	Etiologic Factors			Complications			Splenomegaly	Gallbladder †	Biopsy Findings ‡
					Alcohol	Acute Hepatitis	As Therapy	Hemorrhage	Ascites	Portal Hypertension *			
Group A. Patients with "abnormal" apparent ½ survival time of red cells													
E. F.	60	M	Cirrhosis	5	+	0	0	0	0	0	+	Stones	Cirrhosis 2+
J. C.	52	M	Cirrhosis	15	0	+	0	0	0	+	+	Stones	.....
B. M.	31	M	Cirrhosis	7	0	+	+	0	+	+	+	Stones	Cirrhosis 3+
V. S.	52	F	Cirrhosis	3	+	0	0	0	+	+	0	N.F.	Cirrhosis 3+
J. S.	39	M	Cirrhosis	3	0	+	+	0	0	0	0	Stones	Cirrhosis 2+
R. P.	66	M	Cirrhosis	2	+	?	0	+	0	+	+	N.F.	.....
S. I.	57	M	Cirrhosis	3	+	0	0	0	0	+	+	Normal	.....
J. D.	46	M	Cirrhosis	1	+	?	0	0	+	+	+	Stones	Cirrhosis 3+
Group B. Patients with "borderline" apparent ½ survival time of red cells													
N. F.	48	F	Cirrhosis	6	+	0	0	+	+	+	0	Normal	Cirrhosis 2+
T. Z.	38	F	Cirrhosis	3/12	0	+	0	0	0	0	+	N.F.	Cirrhosis 2+
A. C.	43	F	Cirrhosis	3	0	0	0	0	0	0	+	Stones	Cirrhosis 2+
B. C.	39	F	Cirrhosis	9	0	+	0	0	0	0	+	Normal	Cirrhosis 3+
Group C. Patients with "normal" apparent ½ survival time of red cells													
E. M.	18	M	Acute viral hepatitis	1/12	0	+	0	0	0	0	0	Normal	.....
H. C.	49	F	Chronic biliary obstruction	1	0	0	0	0	0	0	+	..... §	Slight fibrosis, bile plugs
E. K.	48	M	Cirrhosis	6	+	0	0	0	+	0	0	N.F.	Cirrhosis 3+
S. G.	35	M	Chronic hepatitis	9	0	+	0	0	0	0	0	Normal	Chronic hepatitis, minimal
W. G.	57	M	Chronic hepatitis	1	0	+	+	0	0	0	+	Stones	Chronic hepatitis, severe
G. K.	46	M	Cirrhosis	1	+	0	0	0	0	0	+	Normal	Cirrhosis 3+
M. G.	42	F	Cirrhosis	2	+	0	0	0	0	+	0	Normal	Cirrhosis 2+

* The presence of portal hypertension was determined either by esophagoscopic demonstration of varices or by direct measurement of the portal pressure.
† N.F. indicates nonvisualization or poor visualization by the Graham-Cole test.
‡ Cirrhosis was graded as follows: 1+, minimal; 2+, moderate; 3+, marked.
§ Cholecystectomy for stones prior to study.

TABLE 2.—*Laboratory Data*

Patient	Apparent ½ Survival Time, Days	Bone Marrow *	Hematocrit Level, %	Reticulocyte Count, %	Fecal Urobilinogen,† Mg./24 Hr.	Coombs Test	White Blood Cells/ Cu. Mm.	Thrombocytopenia	Liver-Function Tests: Bilirubin, Mg./100 Ml. Direct/Total	Liver-Function Tests: Flocculation Tests	Liver-Function Tests: Sulfobromophthalein ‡	Liver-Function Tests: Alkaline Phosphatase §
Group A. Patients with "abnormal" apparent ½ survival time of red cells												
E. F.	15	++++	24.0	5.8	546	0	4,200	+	0.2/0.4	Pos.	13.4	3.5
J. C.	15	+++	44.6	2.3	277.2	0	3,500	+	0.3/1.9	Pos.	40.8	10.7
B. M.	20	++++	39.0	4.1	128	0	4,250	+	0.79/3.04	Pos.	43.7	8.9
V. S.	21	+	45.0	1.5	70.2	0	7,250	+	0.2/0.5	Neg.	20.4	4.3
J. S.	23	++	47.0	0.5	80.7	0	10,200	0	0.16/0.6	Neg.	14.7	1.7
R. P.	23	+++	42.0	1.4	....	+	3,150	+	0.2/1.0	Neg.	13.4	4.9
S. I.	24	++	43.0	0.6	....	0	4,600	+	0.1/0.7	Neg.	17.0	5.2
J. D.	25	++++	39.0	2.9	119.4	0	7,100	+	0.5/1.7	Neg.	26.2	2.9
Group B. Patients with "borderline" apparent ½ survival time of red cells												
N. F.	26	++	34.0	0.2	54.2	++	4,800	0	0.09/0.14	Pos.	15.0	3.5
T. Z.	26	+	42.0	1.0	56.8	0	4,700	0	4.7/7.8	Pos.	18.3	4.9
A. C.	26	+++	39.0	2.6	12.9	+++	6,600	+	6.7/12.3	Neg.	....	43.3
B. C.	26	....	47.0	0.5	95.7	0	5,250	+	0.4/1.8	Pos.	54.2	7.1
Group C. Patients with "normal" apparent ½ survival time of red cells												
E. M.	27	0	46.0	1.0	29.3	0	6,600	0	1.3/3.1	Pos.	....	7.0
H. C.	27	0	38.0	0.5	95.4	0	5,000	+	0.64/1.46	Neg.	28.7	13.2
E. K.	28	++	44.0	0.6	37.2	0	6,600	0	0.08/0.4	Pos.	13.9	3.6
S. G.	28	0	44.0	0.9	74.2	0	6,500	0	0.1/1.9	Neg.	2.1	2.6
W. G.	31	++	40.0	0.4	77.6	0	5,900	0	0.4/1.2	Pos.	38.1	3.3
G. K.	32	0	46.0	1.5	94.8	0	5,250	+	0.08/0.4	Neg.	2.1	4.9
M. G.	36	0	44.0	0.4	86.2	0	7,500	+	0.13/0.45	Neg.	8.0	6.1

* Bone marrows were graded as to degree of erythroid hyperplasia as follows: slight, +; moderate, ++; marked, +++; very marked, ++++.
† All patients in Groups A and B had four-day stool collections weighing in excess of 500 gm., except for three (V. S., T. Z., and B. C.).
‡ Per cent retention at 45 minutes.
§ Measured in Bodansky units.

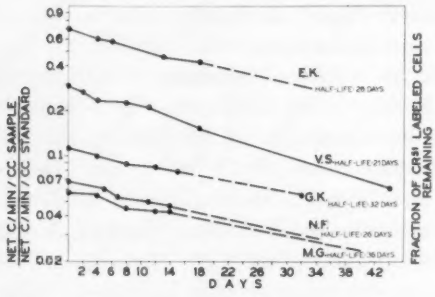


Fig. 1.—Typical curves of the apparent half survival times of five patients with cirrhosis of the liver.

hemoglobin levels and to determine white blood cell and platelet counts. Anemia was considered to exist when the hematocrit level was below 37 in females and below 40 in males.[34] The reported hematocrit value represents an average of from six to nine separate hematocrit determinations taken on various days during the period of investigation. A diagnosis of thrombocytopenia was made when the platelet count was below 150,000 per cubic millimeter by direct count[34] or when below 500,000 per cubic millimeter by a modification of Dameshek's indirect method.[35] The reticulocytes were counted on blood films stained with brilliant cresyl blue and considered to be abnormal when greater than 1.5%. The direct Coombs test was performed on fresh blood at room temperatures, using potent absorbed antisera. Excretion of fecal urobilinogen was determined on four-day stool collections, using Watson's quantitative method,[36] and the results were expressed as milligrams excreted per 24 hours. All stool specimens were routinely checked for occult blood, and the tracer study was not done if they were positive.

Study of the bone marrows was done with a supravital staining technique. The degree of erythroid hyperplasia was roughly estimated by counting the number of nucleated erythrocytic elements per 100 nucleated white cells. These results were arbitrarily expressed as follows: slight erythroid hyperplasia (25 to 30 nucleated erythrocytes per 100 white cells), moderate erythroid hyperplasia (30 to 45 nucleated red cells per 100 white cells), marked erythroid hyperplasia (45 to 60 nucleated red cells per 100 white cells), and very marked erythroid hyperplasia (over 60 nucleated red cells per 100 white cells). In addition, tissue fragments of the bone marrow were studied, and estimates of erythroid hyperplasia in all cases were found to agree with the erythroid count (Table 2).

Serial liver-function tests were performed on all patients, which included quantitative van den Bergh reaction, sulfobromophthalein (Bromsulphalein) test, cephalin-cholesterol flocculation, thymol flocculation and turbidity, zinc sulfate turbidity, ammonium sulfate turbidity, alkaline phosphatase, prothrombin time, and serum cholinesterase.

The gall bladder and biliary tract were studied by the use of the Graham-Cole test or by direct observation in those who underwent surgical exploration.

Ten normal adults without signs of hematologic or hepatic disorders were used as controls. The apparent half survival time of the red cells was determined in these patients, using their own blood, in a manner identical with that used in the study of this group.

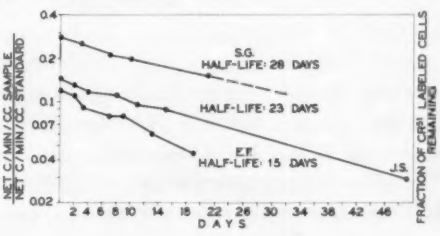
RESULTS

Apparent Half Survival Time of Red Cells.—In the 10 normal controls the average apparent half life of the red cells was found to be 33 ± 3.2 days. Taking two standard deviations, the lower value of normal was 26 days. On the basis of these values the results in the 19 patients studied fall naturally into three groups: Group A, with definitely abnormal values below 26 days; Group B, with borderline values, all exactly 26 days, and group C, with values within the normal range, 27 days or higher (Tables 1 and 2).

There were eight patients in Group A (42%), all of whom had cirrhosis of the liver. There were an additional four patients, also with cirrhosis of the liver, in Group B (21%). The remaining seven patients all had apparent half survival times of 27 days or greater and were placed in Group C. Representative curves from which the apparent half survival time of the red cells was calculated are illustrated (Fig. 1 and 2).

Bone Marrow.—Bone marrow aspirations were done on all of the patients in Group A. All but one of these (V. S.) had moderate

Fig. 2.—Apparent half survival time in one patient with chronic hepatitis (top curve) and two patients with cirrhosis of the liver (middle and lower curves).



or marked erythrocytic hyperplasia. One patient had only slight erythrocytic hyperplasia. Increased amounts of iron deposits were observed in four of this group (B. M., N. F., R. P., and J. D.).

Three of the four patients in Group B had bone marrow studies, and these three patients also had some degree of erythrocytic hyperplasia. In Group C five patients had normal marrows, while the other two had some degree of erythroid hyperplasia. No abnormal iron deposits were seen in any of the patients in Group B or C.

Anemia.—Because of the wide technical errors in counting red blood cells or in measuring hemoglobin, the hematocrit was used to determine the presence of anemia. In Group A there were only three patients having an anemia which was apparent by the hematocrit level (E. F., J. D., B. M.). These three patients showed the most marked bone marrow erythrocytic hyperplasia seen. A reticulocyte level over 1.5% was seen in only four patients in Group A and ranged from a low of 2.3% to a high of 5.8%.

One patient in Group B and none of the patients in Group C had anemia as judged by the hematocrit level. The one patient in Group B (N. F.) had erythroid hyperplasia of the bone marrow. A minimal reticulocyte level of 2.6% was seen in one patient in Group B (Table 3).

Fecal Urobilinogen.—Fecal urobilinogen determinations were done in six of the eight patients in Group A and in all of the patients in Groups B and C. These values are expressed as milligrams excreted per 24 hours and represent determinations of four consecutive days' stool collections. Only one patient had an abnormal value (E. F.), and one had a value at the upper limits of normal (J. C.). Both of these patients were in Group A and their red cells had apparent half survival times of 15 days. One patient (R. P.) had a stool specimen which was positive for occult blood on the day following the injection of the Cr^{51}. Subsequent stool specimens, however, were negative for occult blood. There was no evidence of hemorrhage in any of the other patients.

Coombs Test.—A direct Coombs test was done on all of the patients. These were all negative except for a 1+ reaction in one patient in Group A and a 2+ and a 3+ reaction in two of the patients in Group B. These last two patients had received extensive transfusions of whole blood in the past.

TABLE 3.—*Comparison of Data of Patients with "Abnormal," "Borderline," and "Normal" Apparent Red Cell Half Lives*

Group	Cases, No.	Abnormal Bone Marrow	Anemia	Reticulocyte Counts >1.5%	Leucopenia	Thrombocytopenia	Splenomegaly	Gall-Bladder Disease	
								Stones	NF *
A (abnormal)	8 (42%)	8	3	4	5	7	6	5	2
B (borderline)	4 (21%)	3	1	1	2	2	3	1	1
C (normal)	7 (37%)	2	0	0	0	3	3	1	1
Total	19	13	4	5	7	12	12	7	4

* NF indicates nonvisualization of the gall bladder by x-ray.

White Blood Cell Counts and Platelet Counts.—The white blood cell counts in the patients in Group A ranged from 3,150 to 10,200. Leucopenia was present in five of the eight patients. In Group B the leucocyte count ranged from 4,800 to 6,600 and two of these patients had a leucopenia. All of the patients in Group C had counts above 5,000.

Thrombocytopenia was present in seven of the eight patients in Group A, in two of the patients in Group B, and in three of the patients in Group C.

Liver-Function Tests.—A portion of the battery of liver-function tests performed at the time of the survival study is shown in Table 2. There was no correlation between any of these tests and the apparent half survival time of the red cells.

Splenomegaly.—Splenomegaly was determined by palpation and/or x-ray evidence. The spleen was definitely enlarged in six of the patients in Group A and in three of the patients in Group B. The spleen was also enlarged in three of the patients in Group C.

Gall-Bladder Disease.—Of the eight patients in Group A, only one had a normal gall bladder by x-ray visualization. There were five who had definite calculi and two whose gall bladders were not visualized. In Group B, one patient had stones, one had a nonvisualizing gall bladder, and two had normally functioning gall bladders. Of the seven patients in Group C, only one patient had stones, while one had a nonvisualizing gall bladder and four were normal by the Graham-Cole test. The remaining patient (H. C.) had cholelithias and a cholecystectomy prior to the study. An attempt was made to perform the cholecystograms at a time when the serum bilirubin was near normal and the sulfobromophthalein retention was not excessive, and in many cases this was done after the red cell survival studies (Table 4). On the basis of our previous experience [37] and the experience of others,[38] x-ray visualization of the gall bladder will usually be satisfactory unless liver dysfunction is markedly altered. Only one (T. Z.) of the four patients with nonfunctioning gall bladders had liver-function tests which were sufficiently abnormal at the time of cholecystography to anticipate interference with x-ray visualization.

TABLE 4.—*Liver-Function Tests of Patients with Nonvisualizing Gall Bladders**

Name	Bilirubin, Mg./100 Ml. Direct/Total	Thymol Turbidity, Units †	Sulfobromophthalein ‡	Alkaline Phosphatase §
V. S.	0.43/1.1	1.6	14.9/9.78	5.3
R. P.	0.24/1.16	1.2	13.4/—	3.8
T. Z.	0.54/1.2	7.7	18.3/11.1	7.2
E. K.	0.08/0.33	1.0	6.1/—	2.7

* These tests were performed at the time of cholecystogram and not during the red cell survival study. Iodopanoic acid (Telepaque) was used as the dye.

† A curve with a normal value of 2 units was employed for the thymol-turbidity determinations.

‡ Per cent retention at 45 and 60 minutes.

§ Measured in Bodansky units.

TABLE 5.—*Significance of Association Between Abnormal Values for Apparent Half Survival Time of Red Cells and Other Factors in Clinical Syndrome, as Tested by χ-Square Test*

	Half Survival Time		
	Abnormal	Normal	*P*
Splenomegaly present	6	6	NS
Splenomegaly absent	2	5	
Cirrhosis present	8	7	0.01
Cirrhosis absent *	0	14	
Leucopenia present	5	2	NS
Leucopenia absent	3	9	
Thrombocytopenia present	7	5	<0.05
Thrombocytopenia absent	1	6	
Erythroid hyperplasia present	8	5	0.01
Erythroid hyperplasia absent	0	6	

* Includes the 10 normal persons studied by the same method.

Significance.—In an attempt to determine the significance of some of these findings, part of the data was tested by the χ-square test (Table 5). For the purpose of this evaluation only those patients whose apparent half survival time was below 26 days, i. e., Group A, were considered as having abnormal curves. Those patients with half survival time of the red cells of two standard deviations or less, i. e., Groups B and C, were considered as having "normal" apparent half survival time of the red cells. It can be seen that the occurrence of the "abnormal" red cell survival curves in cirrhosis is not due to chance alone. Also, the occurrence of thrombocytopenia or erythroid hyperplasia in the marrow is not due to chance alone. However, the incidence of splenomegaly in cirrhosis does not differ from that in other liver diseases at a 95% level of confidence.

COMMENT

It is clear from these observations that increased hemolysis is a frequent occurrence in chronic liver disease and is much commoner than has previously been thought. Eight cases, or 42% of the entire group and 53% of those with cirrhosis, had an abnormal apparent half survival time. In four additional cases the values fell exactly two

standard deviations from the mean, and, although these have been considered within the normal range for statistical purposes, it is not unlikely that they represent abnormal values. This possibility is supported by the finding of erythrocytic hyperplasia in three of these four. The size of the sample is inadequate for conclusions regarding the incidence of increased hemolysis as related to the type of liver disease, although the data suggest that cirrhosis is important. The etiology of the cirrhosis would appear to be irrelevant.

The first question that naturally arises concerns the practical significance of results obtained by this method. Although we are not able to express the values in terms of absolute increase in red cell turnover, the results are statistically significant. Also, the presence of erythrocytic hyperplasia in the bone marrow and the high number of gallstones speaks for a significant degree of increased hemolysis, even if it was not enough to cause anemia in all cases.

The absence of anemia in five of the eight patients with "abnormal" curves is not surprising when we consider that the bone marrow is able to compensate for a very considerable increase in the rate of red cell destruction. Thus, all of our eight patients showed some degree of erythroid hyperplasia in the bone marrow. A similar lack of correlation between bone marrow changes and the presence of anemia has also been observed by Berman and co-workers.[14] Evidence of the ability of the bone marrow to compensate for increased red cell destruction has been obtained by Crosby and Akeroyd.[39] They studied two cases of hereditary hemolytic anemia and demonstrated that anemia appeared only when the total survival time was less than 15 to 20 days. They concluded that the bone marrow in their cases was capable of producing about seven times the normal output of hemoglobin. This suggests that anemia only appears when the rate of hemolysis is rather markedly increased.

The explanation for our failure to find more cases with an elevated fecal urobilinogen is not readily apparent. It is of course possible that this is not a sufficiently sensitive measure of the rate of red cell destruction. Thus, Brown [40] found normal values for the fecal urobilinogen and the reticulocyte counts in six patients with various nonhepatic diseases who, by the Ashby technique, had abnormal red cell survival times. On the other hand, it seems not unlikely that the presence of severe liver damage may interfere with the excretion of bile pigments and thus alter the significance of the fecal urobilinogen determination. This explanation is supported by the finding of hyperbilirubinemia involving either the prompt direct or the total fraction in five of the six abnormal cases in which the fecal urobilinogen was determined and in three of the four "borderline" cases. It is also of interest that the one case with the highest fecal urobilinogen was also that of the person with the least amount of liver damage as indicated by both biopsy and laboratory findings.

We have no direct evidence regarding the mechanism of the hemolytic process in these cases. However, in view of the frequent association of splenomegaly, thrombocytopenia, and leucopenia, the best explanation appears to be the so-called hypersplenic syndrome. This could well be secondary to portal hypertension, which was proved in six of the eight "abnormal" cases, either by the demonstration of esophageal varices by esophagoscopy or by direct venous pressure measurements at surgery.

It is obvious that these findings have many important implications. The significance of hyperbilirubinemia in every case of liver disease must be interpreted in the light of a possible hemolytic factor. Only a relatively small increase in the amount of bilirubin presented to the liver may, in the presence of liver disease, result in significant elevation of the serum bilirubin level. This will be especially marked if hyperbilirubinemia is already present. Although we have only made observations in one case of acute hepatitis, it is not unlikely that increased hemolysis may occur here too. This would explain why higher levels of serum bilirubin are seen in acute hepatitis than in extrahepatic obstructive jaundice. Likewise, these findings

provide an explanation for the macrocytic anemia of chronic liver disease, although other factors may also play a role.

The high incidence of gallstones is of particular interest. For some years we have been impressed with the frequency of gallstones in persons with liver disease. It would now appear that this is not a coincidence but that the stones may be the result of a hemolytic process which might well be transitory or intermittent. More important, however, is the possibility that the presence of gallstones, perhaps because of an associated cholangitis, may be an important contributing factor towards chronic progressive liver disease.

Finally, these findings may explain in part the observed effect corticotropin and cortisone in certain cases of liver disease. Perhaps the most striking effect of these steroids is the sharp reduction in the serum bilirubin level.[41] If the hyperbilirubinemia is in part the result of increased red cell destruction, then these steroids might well produce their effect, at least in part, by altering the hemolytic process rather than by acting on the liver.

CONCLUSION AND SUMMARY

Apparent half life survival time of the red cells was determined in 19 patients with liver disease. Fifteen patients had various types of cirrhosis; 1 had acute infectious hepatitis; 2 had chronic hepatitis, and 1 had chronic biliary obstruction.

Abnormal apparent half life survival time of the red cells was found in eight of the patients studied, and borderline values were found in four more. All these 12 patients had cirrhosis of the liver.

Only three of the patients with abnormal red cell survival times had anemia.

All eight of the patients with abnormal apparent half life survival time of the red cells had erythroid hyperplasia of the bone marrow.

The reticulocyte count and the fecal urobilinogen determinations were not delicate enough to detect the degree of hemolysis present in these cases.

The frequent association of thrombocytopenia, leucopenia, and splenomegaly would suggest that the hemolysis is due to a hypersplenism syndrome.

A high incidence of gall-bladder disease was found in patients with abnormal apparent half life survival time of the red cells.

The importance of these results in relation to the interpretation of the serum bilirubin level and other laboratory and clinical findings in liver disease is discussed.

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SCLERODERMA

Pulmonary and Skin Studies Before and After Treatment with Cortisone

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GENERALIZED scleroderma is recognized as a disseminated disease which may involve not only the skin but many other organs. It is usually a chronic illness with a gradual downhill progression and lasts from months to years.

GENERAL OBSERVATIONS

The course of scleroderma can be divided into two phases: the first is characterized by Raynaud-like phenomena; the second is initiated by the appearance of constitutional symptoms, including malaise, myalgia, and arthralgia and later is characterized by the development of visceral manifestations. These later phenomena result from the structural and functional derangements consequent to the degeneration of parenchymal cells and the simultaneous proliferation of connective tissue, in such diverse systems as skin, subcutaneous tissue, muscle, tendon and fascia, bones, blood vessels, serous surfaces, internal organs, endocrine glands, and the nervous system. These widespread and continuing alterations, resulting at least in part from the proliferation of fibrous tissue, have led Goetz [1] to propose the name "progressive systemic sclerosis" to replace that of scleroderma. The widespread connective tissue alteration in scleroderma, together with certain clinical features common to such diseases as disseminated lupus erythematosus, polyarteritis, and dermatomyositis, has led to its inclusion in the group of diseases designated by Klemperer as "collagen diseases." [2] However, no definite relation to this group has been established other than the apparently similar disturbances of the connective tissue.

Pulmonary involvement by scleroderma has been known for half a century, and many detailed pathological and, more recently, roentgenological descriptions have appeared. Pulmonary symptoms may coincide with cutaneous manifestations or, occasionally, precede them.[3] In general, however, Raynaud's phenomena or cutaneous involvement will be established before pulmonary involvement appears.

Pathology.—In 1891, Finlay * recognized the association between scleroderma and pulmonary fibrosis. In 1898, von Notthafft [4] described pulmonary changes found at necropsy in patients with scleroderma. Many pathological studies of the pulmonary findings in scleroderma followed. Getzowa [5] described two types of pulmonary changes in great detail: (1) cystic sclerosis and (2) compact pulmonary sclerosis. The former was characterized by hyaline degeneration of the alveolar walls in some areas of the lung, causing the capillaries to disappear. As these hyalinized walls became thinned and ruptured they gave rise to cysts in the subpleural region, which were usually epithelized. The compact pulmonary sclerosis developed in other areas, especially the bases, where diffuse alveolar wall fibrosis progressed, with the obliteration of capillaries and of alveolar

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* Finlay, D. W., cited by Church and Ellis.[6]

spaces. Church and Ellis [6] have also described cystic pulmonary fibrosis in scleroderma. Bevans [7] found a marked discrepancy in one of her cases between anatomic lesions and clinical and radiological findings. Dostrovsky's [8] pathologic report of two cases described alveolar distention, occasionally assuming cystic dimensions, in the cortical and subcortical regions of the upper part of the lung, with atelectasis at the bases. The fibrotic changes in the pulmonary tissue made the involved lobes grossly firm, inelastic, and small. Fibrous pleurisy involving the lower portions of the lung was reported by Baehr and Pollack.[9]

In addition to the above changes, Spain and Thomas [10] described bronchial involvement in scleroderma leading to bronchiectasis and bronchiolectasis. This was thought to be due to fibrous replacement of the muscular coat of the bronchial tree similar to the atrophy and fibrosis of musculature seen in scleroderma of the gastrointestinal tract. Damage to the musculoelastic layer of the bronchial tree would interfere with maintenance of its caliber and tonus and lead to bronchiectasis and bronchiolectasis. Contributory factors in its development would be secondary infection, which is frequently seen in pulmonary scleroderma, and diffuse parenchymal fibrosis, which exerts traction on the smaller bronchioles.

Roentgenographic Diagnosis.—The roentgenologic picture of pulmonary scleroderma is distinctive, and the diagnosis may sometimes be made without knowledge of the clinical manifestations. Murphy and coworkers [11] reported the first case in which the pulmonary changes of scleroderma were diagnosed by roentgenogram during life. Early, there is a slight diffuse network-like shadow, which extends from the cardiac border to the periphery in the basal areas only. When the process is more advanced, the interlacing linear shadows become more marked and involve the lower two-thirds of the lung fields. Scattered irregular mottled shadows may be present. The apices and the outer border of the basal areas usually remain clear. Cysts and diaphragmatic irregularity due to adhesions have been described.†

Roentgenologically, pulmonary scleroderma must be differentiated from sarcoidosis, lymphangitic carcinomatosis, pulmonary congestion, and pulmonary fibrosis from other causes.[10] Sarcoidosis is usually associated with bilateral hilar adenopathy, which is rare in scleroderma. The fibrosis of scleroderma tends to be more discrete and linear than the fuzzy vascular markings seen in congestive failure. When pulmonary changes occur in polyarteritis nodosa, the roentgenogram shows diffuse miliary and nodular infiltrations, and, characteristically, serial x-ray studies reveal a continually changing picture, new lesions appearing while others are healing. Pulmonary involvement in disseminated lupus erythematosus consists only of pleural effusion. Rheumatic pneumonia may show vascular congestion, pulmonary consolidation with or without pericardial effusion,‡ or pulmonary edema only. The pneumoconioses produce a nodular fibrosis predominantly in the upper and outer portions of the lung rather than the thin linear type of fibrosis in the lower, inner portions of the lung that is seen in scleroderma.

Pulmonary Function Studies.—The functional changes that occur in scleroderma of the lungs include both ventilatory and respiratory disturbances.§ Ventilatory function, or the movement of air in and out of the lungs, may be impaired by involvement of the skin and muscles of the thorax interfering with chest motion; by involvement of the diaphragm; by fibrous contraction of the pleura which, in turn, compresses the lung tissue, or by diffuse peribronchial fibrosis which leads to obstructive emphysema. Such changes result in a diminished vital capacity and maximal breathing capacity, an increased residual volume, and an increased residual volume/total lung capacity ratio.

Gas exchange, or respiratory function, however, is more impaired than ventilatory function. The widening of alveolar septa,

† References 8 and 11-16.
‡ References 16 and 17.
§ References 10 and 18.

thickening of blood vessel walls, and obliteration of vascular lumina that occur in scleroderma cause interference of gas exchange across the alveolar septum.

Treatment.—The recent use of corticotropin and corticosteroid hormones in the treatment of collagen disorders has produced dramatic results in some instances. In the treatment of scleroderma, however, the introduction of these agents has resulted in conflicting reports as to its beneficial effects. Hines and co-workers [19] treated two patients with corticotropin (ACTH). There was temporary improvement, but symptoms recurred two to three weeks after the drug was discontinued. Bayles and co-workers [20] treated four patients with corticotropin, and all four improved. However, symptoms returned two to three weeks after treatment was stopped. Lunseth and co-workers [21] reported a fulminating change from a chronic to an acute course during treatment with corticotropin. The patient died after having received 475 mg. of corticotropin intramuscularly. Autopsy showed severe fibrinoid necrosis of the renal glomeruli to be the cause of death. Sharnoff and co-workers [22] treated one patient with diffuse scleroderma with 100 mg. of cortisone daily for two months. The patient responded dramatically, but after 10 weeks hypertension, uremia, and death followed. Autopsy showed severe and presumably accelerated kidney lesions.

One case of scleroderma with pulmonary involvement was treated by West and co-workers [23] with cortisone for 20 days. Although the skin became less indurated, no improvement in the pulmonary lesions and pulmonary function were observed by roentgenograms and by pulmonary function tests. Beigelman and co-workers [12] recently treated nine patients with scleroderma, five of whom showed pulmonary lesions, with corticotropin and cortisone. These authors concluded that "no more than mild, transient improvement could be attributed to these agents." Severe hypertension and nephrosclerosis developed immediately after corticotropin therapy in one patient who died from a cerebrovascular hemorrhage. One patient with pulmonary involvement seemed to have been benefited by maintenance therapy with cortisone over a 30-month period.

PRESENT STUDY

The scarcity of pulmonary function studies in patients with scleroderma who were being treated with corticotropin or cortisone prompted us to report our observations on the effect of cortisone in three patients with generalized scleroderma who had prominent involvement of the lungs.

Pulmonary function studies, including lung volume measurements, ventilation studies, and determinations of arterial blood gases, were made before and after treatment with cortisone. Techniques used in these measurements have been described previously.[24] Other laboratory studies, including x-ray, electrocardiograms, and skin biopsies, were made on each patient before and after therapy.

Care was taken to exclude the presence of a complicating infection, especially tuberculosis, prior to starting treatment. Cortisone ‖ by mouth was given for 35 days to each patient, with a dose of 300 mg. for 3 days, followed by 200 mg. for 5 days, and 100 mg. daily for 27 days.

One gram of oxytetracycline (Terramycin) ¶ and 1 gm. of potassium chloride were given daily, and a low-salt diet was maintained during treatment.

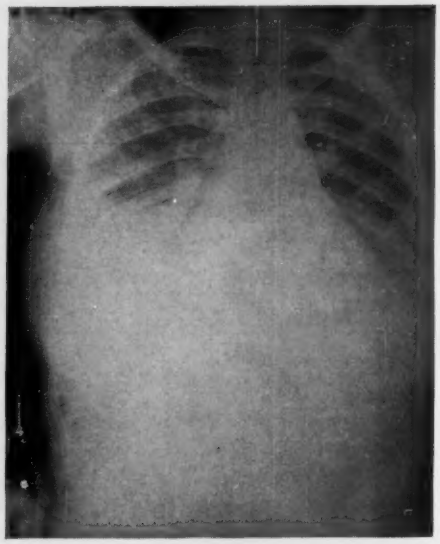
REPORT OF CASES

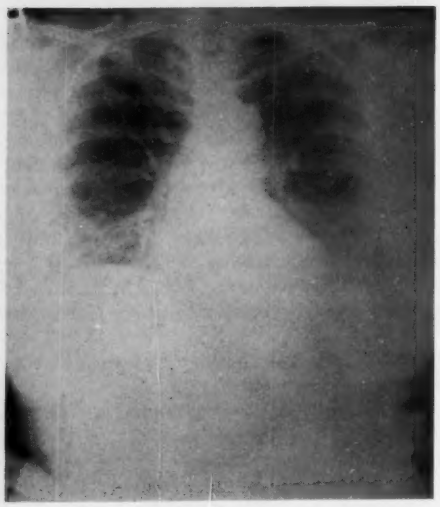
PATIENT 1.—P. G., a 40-year-old Negro housewife, was admitted to the Boston City Hospital in July, 1953, because of marked weight loss, increasing dyspnea on exertion, cyanosis of the lips and fingernails, fatigue, and progressive skin changes. During 1952 she developed mottled depigmentation of forearms and upper anterior chest, blueness and coldness of the fingers on exposure to cold, chronic cough, tiredness, and moderate exertional dyspnea.

On physical examination, the skin over the hands and forearms was tight, dry, shiny, firm, and slightly bound down and the finger tips were pitted. There

‖ Kindly supplied through the courtesy of Merck & Company, Inc., Rahway, N. J.

¶ Kindly supplied through the courtesy of Pfizer Laboratories, Division of Chas. Pfizer & Company, Inc., N. Y.





was marked clubbing of the fingers. There were harsh breath sounds over both lung fields and fine rales at the bases. The heart was enlarged, and no murmurs were heard. There was a sinoauricular tachycardia, with a rate of 107 per minute. The electrocardiogram was borderline normal. Blood cell counts, urinalysis, and blood chemistry studies were within normal limits. The serum albumin-globulin ratio was 3.2:4.2, and the blood Wassermann test was positive (neurosyphilis, treated). Chest x-ray showed an increase in linear markings, with infiltration of the peribronchial tissue in a reticular pattern involving the lower two-thirds of the lungs, small nodular densities about 2 mm. in diameter in the same area, and prominent hilar shadows. The heart was enlarged to the right, and there was a prominence of the pulmonary conus (Fig. 1). A barium esophagogram showed narrowing of the distal esophagus and a lack of normal contractions. X-ray of the hands revealed concave defects involving the distal ends of the distal phalanges of several fingers.

Skin biopsy from the left forearm prior to treatment showed moderate dermal fibrosis (Fig 2). The histopathologic examination of some mediastinal nodes taken from the vicinity of the right hilum showed a nonspecific inflammation.

Pulmonary function studies indicated marked arterial oxygen unsaturation after exercise and moderate impairment of ventilation.

In September, 1953, the patient was treated with cortisone by mouth for 35 days, as described above. The course of therapy was accompanied and followed by moderate subjective symptomatic improvement, with softening of the skin and minimal improvement of pulmonary function studies. The esophagogram showed a return to more normal function.

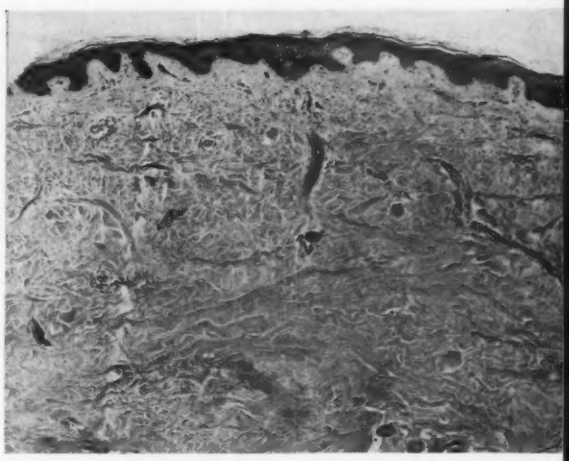
Laboratory examinations were unchanged except for the improved serum albumin-globulin ratio, which was 3.3:2.3. X-ray showed no significant change in the lungs. Skin biopsy from the left forearm showed insignificant histopathologic changes.

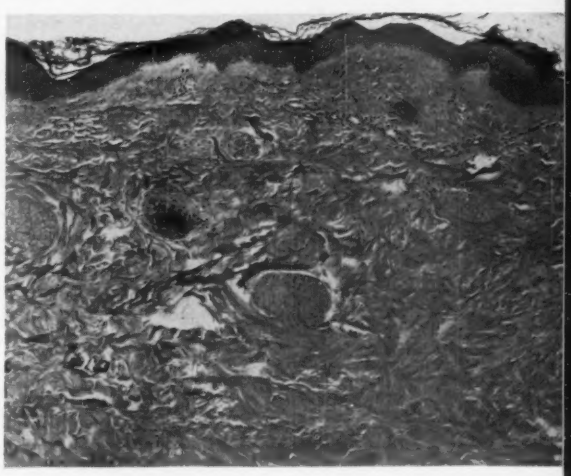
PATIENT 2.—A. M., a 32-year-old Negro housewife, entered the Boston City Hospital in July, 1951, because of tightness of her skin of one year's

Fig. 1.—*A* (Patient 1; P. G.), there is a coarse mottling with miliary distribution, involving the lower two-thirds of both lungs, and an increase in the bronchovascular markings throughout, with marked accentuation of the hilums. There is moderate widening of the heart transversely, more to the right, which may represent right ventricular enlargement. The diaphragms and pleural reflections appear normal. *B* (Patient 2; A. M.), the diaphragms are obscured by overlying breast shadows. There is a bilateral increase in the bronchovascular markings, and changes consistent with fibrosis or chronic infection are present in both bases. The heart is slightly enlarged to the right. *C* (Patient 3; R. P.), there is an increase in the bronchovascular markings in both lung fields and prominence of the hilums. The diaphragm and pleural reflections appear normal.

duration. The feeling of tightness began in her hands and gradually spread up her arms to her chest. Six months after the onset of symptoms she began to experience numbness, tingling, coldness, and blanching of her fingers, often precipitated by exposure to cold; from time to time she noted small ulcers on her finger tips which became crusted, leaving small pitted scars. The skin of her face became tight, and she developed exertional dyspnea and orthopnea. She had two miscarriages in the past two years early in the course of pregnancy. In April, 1953, she was admitted to the hospital because of increasing dyspnea at rest and on exertion, chronic productive cough, cyanosis of lips and fingernails, and progressive skin changes. The patient was in her fourth month of pregnancy at the time of admission, and her difficulties seemed to have become more accentuated with the advancement of her pregnancy.

On physical examination, characteristic scleroderma changes were apparent. The skin over her face, upper extremities, and upper chest was tight and shiny; small pitted scars were present on the finger tips of the right hand and middle finger of the left hand. Both legs were edematous, with dusky erythema and induration of the skin from the ankles to just below the knees. The skin was very tight and shiny over her abdomen and breasts, causing a great deal of pain. There was mild cyanosis and clubbing of the fingers. The respiratory rate was markedly increased. Moderate wheezing on expiration and a few moist rales were heard at the bases. There was a sinoauricular tachycardia, with a rate of 120. A loud second pulmonic sound but no murmurs were heard. The blood pressure was 130/78.





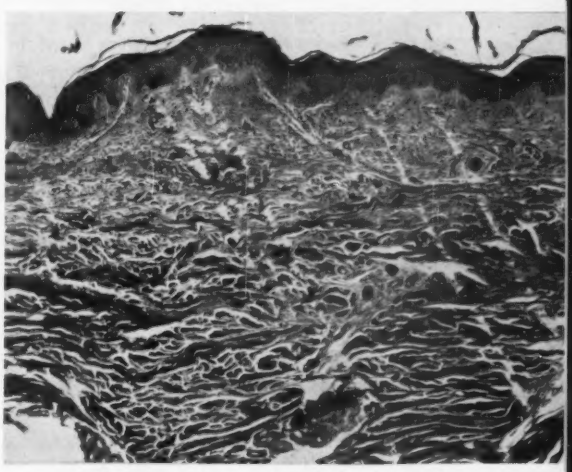


Fig. 2—*A* (Patient 1; P. G.), skin biopsy specimen from forearm prior to treatment, showing some atrophy of the epidermis. There is a little relative hyperkeratosis, and the collagen is more dense, homogeneous, and acidophilic than normal. Hair follicles and sebaceous glands are absent. A few small coil glands are still present in the deeper layers of the cutis, and a few blood vessels are present in this section. Some of the small arterioles have thickened walls. *B* (Patient 2: A. M.), skin biopsy specimen from a calf, a year prior to treatment, showing slight atrophy of the epidermis. There is an increase in the density and homogenization of the collagen and a loss of the dermal appendages, particularly the hair follicles and sebaceous glands, with atrophy of the sweat glands. There are very few blood vessels, and the one shown here has a thickened wall with narrow lumen, with a very slight amount of perivascular infiltrate, consisting chiefly of lymphocytes. *C* (Patient 3, R. P.), skin biopsy specimen from arm, prior to treatment, showing marked atrophy of the epidermis, with relative hyperkeratosis. The collagen is more dense, homogeneous, and acidophilic than normal. There is loss of the dermal appendages, with dilated vessels, in the upper part of the cutis, which are lined with a single layer of cells and devoid of perivascular infiltrate (telangiectases). This represents a well-developed late stage of scleroderma.

Blood cell counts, urinalysis, and blood chemistry studies were within normal limits. Chest x-rays showed elevation of the diaphragm, increased vascular markings, and a fine net-like infiltration in the middle and lower lung fields. The apices were clear. The heart was enlarged to the right, and there was prominence of the pulmonary conus (Fig. 1). A barium study of the esophagus showed a lack of normal contractions, and there was narrowing in the distal portion. The rest of the gastrointestinal tract was roentgenologically normal. Pulmonary function studies indicated impairment of ventilation and lung volumes and slight arterial oxygen unsaturation. Skin biopsies were taken from several involved areas and showed advanced sclerodermatous changes (Fig. 2). In May, 1953, the patient was treated with cortisone by mouth for 35 days.

Soon after treatment was started there was marked improvement in the skin. It became softer and more flexible, especially over the protruding abdomen, which resulted in great relief to the patient. Her dyspnea became less pronounced and her cough improved. The patient was able to carry on with her pregnancy and was delivered of a healthy infant. No untoward effects to the infant as a result of the cortisone treatment were demonstrable. After treatment was completed the esophagus appeared normal. A follow-up x-ray of the lungs and skin biopsy showed no significant changes.

Signs of relapse occurred nearly six months after completion of treatment. This delay in relapse was possibly due to an increased endogenous cortisone effect associated with pregnancy.

PATIENT 3.—R. P., a 54-year-old white housewife, was first seen at the Boston City Hospital in July, 1950, because of discoloration and stiffness of her left hand and forearm of five months' duration. Two years previously she had first noted tingling of the left hand, without other signs or symptoms. On the lateral surface of the left forearm was a well-demarcated area of smooth shiny hard indurated skin with areas of hyperpigmentation and atrophy. The skin over the left hand was diffusely firm, and there was some limitation of motion of the hand and wrist.

During the ensuing three years, the skin lesions extended over the lateral surface of her left arm to the posterior aspect of the shoulder, and there was progressive immobility of the left hand, associated with coldness and tingling on exposure to cold. During the third year she noted progressive skin changes on the right hand and arm and on both legs, with stiffness of the right wrist and of both ankles. She had no other symptoms except for a hacking cough and moderate exertional dyspnea present for two years without change.

The physical examination revealed the skin changes described above. Harsh breath sounds were heard over both lung fields, more pronounced at the bases. There were no rales. The blood pressure was 120/80, and the electrocardiogram was within normal limits. A chest x-ray showed increased vascular and bronchial markings and a diffuse mottling of both lower lung fields. The apices were clear, and the heart was within normal limits (Fig. 1). Roentgenographic examination of the gastrointestinal tract showed no involvement. Blood cell counts, urinalysis, and blood chemistry studies were within normal limits except for the serum albumin-globulin ratio of 3.1 : 4.3.

Skin biopsy from the left arm was consistent with moderately advanced scleroderma (Fig. 2). Pulmonary function studies indicated only minimal impairment.

In October, 1953, the patient was given cortisone by mouth for 35 days, as described above. There was a general improvement of her symptoms, better exercise tolerance, and less dyspnea. The hacking cough disappeared entirely. There was softening and increased flexibility of the skin, with a marked increase in mobility of the joints in the areas involved. There was no change in the pulmonary lesions as seen by x-ray. Skin biopsy from the same area as the first biopsy showed no changes histologically. All other examinations remained the same except for the reversal of the albumin-globulin ratio to 3.9 : 2.6.

Two months after treatment was terminated there was a relapse of the skin changes at the ankles; the improvement in the upper extremities remained present for an additional two months but then relapsed also.

COMMENT

Clinical findings common to all three patients, in addition to the skin changes, were severe exertional dyspnea, cyanosis, a dry nonproductive hacking cough, weakness, anorexia, fatigue, and a marked loss of weight during the progress of the disease.

X-rays of the lungs showed an increase in linear markings and peribronchial infiltration of the parenchyma throughout both lung fields, involving primarily the lower two-thirds, with a marked increase in density at the lung roots. There was apparently no involvement of the apices. The lesions showed the characteristic peribronchial and vascular distribution consistent with scleroderma of the lungs.

The right heart enlargement and the prominence of the pulmonary conus in Patients 1 and 2 suggested early cor pulmonale, but the lack of other symptoms made the diagnosis

difficult. Electrocardiographic findings were within normal limits.

Pulmonary scleroderma may show various disturbances, of which fibrosis is the commonest. Depending on the degree, extent, and location of fibrosis, alveolar destruction, vascular involvement, etc., the pulmonary function tests will show minimal to severe abnormalities.

The lung volume measurements (Table 1) revealed findings similar to those of chronic pulmonary fibrosis with compensatory emphysema. The total lung capacity as well as the ratio of residual volume to total lung capacity were elevated and the vital capacity was diminished in two of the three patients. These static measurements were not materially altered by a prolonged course of treatment with cortisone.

The ventilation studies (Table 2) showed some slight disturbances but none of significant degree. The index of intrapulmonary mixing was normal in two of the three patients. Likewise, the maximal breathing capacity was moderately decreased in only one patient.

The arterial blood studies (Table 3) suggested diffusion difficulty for oxygen but not for carbon dioxide, which is more readily diffusable and requires greater ventilatory or membrane defects in order to deviate. There was no disturbance of the acid-base balance. The absence of severe ventilatory disturbances in our patients was rather surprising;

TABLE 1.—*Lung Volume Measurements in Three Female Patients*

Patient	Age, Yr.	Color		Body Surface, $M.^2$	Tidal Vol., L.	Vital Capacity, L.	% Predicted Vital Capacity	Residual Vol., L.	Total Lung Capacity, L.	% Predicted Total Lung Capacity	R.V./T.L.C. × 100
P. G.	40	N	Before therapy	1.54	0.583	2.375	83.70	1.831	4.206	113.52	43.50
			After therapy	1.54	0.768	2.048	71.70	1.252	3.800	102.61	32.95
A. M.	34	N	Before therapy	1.78	0.508	1.554	52.29	4.361	5.915	159.22	73.73
			After therapy	1.90	0.515	1.073	36.10	3.258	4.331	116.58	75.23
R. P.	57	W	Before therapy	1.42	0.334	2.906	120.11	1.815	4.721	112.14	38.40
			After therapy	1.42	0.720	2.504	111.64	2.059	4.563	108.39	45.12

TABLE 2.—*Ventilation Studies*

Patient		Respiratory Rate	Resting Ventilation, L./Min.	Maximal Breathing Capacity		Ventilatory Reserve, %	Index of Intrapulmonary Mixing (% N)
				L./Min.	% Predicted		
P. G.	Before therapy	15	5.68	53.00	65.00	83.0	1.76
	After therapy	16	7.98	86.73	108.50	85.8	1.22
A. M.	Before therapy	21	5.99	99.41	101.20	89.3	6.90
	After therapy	22	6.23	82.14	81.89	86.2	5.14
R. P.	Before therapy	14	3.23	84.90	134.90	94.4	1.32
	After therapy	11	5.57	78.74	125.18	90.0	1.38

TABLE 3.—*Arterial Blood Studies and Alveolar Gases*

Patient		O_2 Content, Vol. %		O_2 Saturation, %		CO_2 Content, Vol. %		pH		Alveolar Gases	
		Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	pCO_2, Mm. Hg	pO_2, Mm. Hg
1, P. G.	Before therapy	14.91	9.89	97.01	64.35	43.21	49.32	7.40	7.39	48.40	65.50
	After therapy	18.85	12.63	92.77	62.16	46.92	47.52	7.37	7.31	39.28	95.35
2, A. M.	Before therapy	13.93	14.39	82.67	85.40	46.48	46.96	7.40	7.42	35.83	96.97
	After therapy	14.08	14.48	85.02	87.44	48.71	48.35	7.42	7.40	41.72	89.65
3, R. P.	Before therapy	21.02	22.29	93.80	99.46	48.83	46.94	7.42	7.40	46.71	93.57
	After therapy	17.16	20.89	76.10	92.64	51.60	48.66	7.39	7.39	37.30	102.32

ventilation is affected not only by the intrinsic pulmonary pathology but much more by the involvement of the skin over the chest, which restricts chest motion. Pulmonary fibrosis is expected to cause decreased vital capacity and also decreased total lung capacity. However, when it is present for a long period of time in combination with various degrees of bronchoconstriction, secondary emphysema is to be expected. There follows an enlargement of the functional residual capacity and the total lung capacity and thus an increased ratio of residual volume/total lung capacity.

The pulmonary function studies in Patient 2 (A. M.) were complicated by the fact that she was pregnant. Gaensler and co-workers [25] have demonstrated that there is a progressive decrease of the vital capacity, maximal breathing capacity, functional residual capacity, and total lung capacity with the progress of normal pregnancy.

Raynaud's phenomenon preceded the symptoms of pulmonary involvement in all three patients. The sclerodermatous changes in the skin involved the upper extremities, the sternal area of the chest, and neck and face, the lower extremities, and in Patient 2 the thighs and abdominal wall as well. The skin was tight, dry, and shiny and was pigmented in the white patient and depigmented in the Negro women. This hardening of the skin produced a severe limitation of motion of the joints in the areas involved. Patients 1 and 2 had narrowing of the distal esophagus, with a decrease of peristalsis. These patients had no difficulties in swallowing, and there was no other evidence of gastrointestinal involvement. The constrictive changes could not be demonstrated by visualization of the esophagus after therapy.

The inverted albumin-globulin ratio in Patients 1 and 2 returned to normal limits after treatment.

After treatment there was definite improvement in the clinical picture. A marked increase in exercise tolerance and decrease in dyspnea was noted by all. The hacking cough disappeared in two and improved in one. The skin was softer; it lost its dry appearance and became warmer to the touch. There was improvement in the performance of movement in all areas involved, such as opening the mouth, closing the fist, etc. Raynaud's phenomenon persisted, but there was better tolerance to cold as measured by cold running water. The skin did not show significant histopathologic changes after treatment, and no significant changes in the diffuse lesions of the lungs could be demonstrated by x-ray after treatment was terminated.

Patient 2, who was pregnant, was very uncomfortable, short of breath, and unable to lie on her back. Several days after treatment was started there was a marked relaxation of the skin, and the patient improved sufficiently to carry on with her pregnancy. The infant showed no apparent side-effects resulting from treatment with cortisone. This has also been noted elsewhere.[26]

In these three patients the treatment with cortisone had a temporary favorable effect upon the skin, but relapse occurred after from three to six months. We did not observe any increase in the rate of progress of the disease following the treatment. The beneficial effect upon the esophageal lesions is not clear, and its occurrence will have to be further investigated. It is apparent that a short course of treatment results in temporary improvement only, with early relapse.

At this time, it seems to us that the administration of cortisone for scleroderma is indicated in those cases in which the site and extent of involvement portends serious consequences.

SUMMARY

Generalized scleroderma with pulmonary involvement in three female patients is described.

Cortisone was given, orally, to all patients for 35 days, for a total dose of 4.6 gm.

Clinical studies, including x-ray and pulmonary function studies, were carried out before and after treatment, to evaluate the effect of cortisone therapy.

Objective and subjective improvement of varying degrees occurred in all patients. The

skin lesions appeared to be more responsive than the visceral ones.

Improvement of the dermatological manifestations was temporary, and relapse occurred in all three patients four to six months after therapy had been terminated.

Pulmonary function studies were not significantly altered by treatment.

No acute exacerbation of the disease occurred in these patients as a result of cortisone therapy.

One patient in the fifth month of pregnancy was started on the 35-day course of treatment and was delivered of a healthy infant. There was no obvious ill effect on either mother or child.

Dr. Donald B. Darling, Resident, Department of Radiology, Boston City Hospital, gave help in the interpretation of the x-ray findings, and Mrs. Dorothy Belgard and Mrs. Doris Koss gave technical assistance.

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DISSEMINATED CANDIDIASIS

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CANDIDA is frequently present as a commensal in the mouth, vagina, and intestinal tract or as a secondary invader following bacterial infections; it may, however, under certain circumstances become of primary clinical importance.

The clinical and pathological entities of localized cutaneous, vaginal, pharyngeal, bronchopulmonary, and pulmonary candidiasis are now well recognized.* Candidemia with mycotic lesions in the viscera has only rarely been reported.† Most of these reports have been on cases of meningitis and endocarditis.‡

The purpose of this paper is to report three cases of disseminated candidiasis observed at the Winnipeg Municipal Hospitals within a period of one year; in two of these patients the organism was isolated from the blood during life. We were particularly interested in the circumstances under which candidemia occurred and in the follow-up of one patient who survived.

REPORT OF CASES

CASE 1.—Mrs. M. C., a 22-year-old housewife, was in good health until three days prior to admission, on Dec. 14, 1952. Examination showed typical findings of nonparalytic poliomyelitis; temperature was 101 F.; pulse rate, 120, and respirations 20 per minute. Hemoglobin was 14.4 gm. per 100 ml.; WBC, 11,450 per cubic millimeter, of which 17% were lymphocytes, 77% polymorphs, and 6% monocytes; sedimentation rate was 14 mm. in an hour (Westergren); urinalysis, normal. Spinal fluid was clear, with 430 white blood cells per cubic millimeter and 100 mg. protein per 100 ml.

By Dec. 16 she had developed extensive paralysis of arms and legs as well as inability to swallow and dyspnea. Vital capacity fell to 250 cc., and she was placed in a tank respirator. She became confused. Intravenous administration of 10% invert sugar and Darrow's solution was started through an indwelling polyethylene tube.

Penicillin, 500,000 units, and oxytetracycline (Terramycin), 1 gm. daily, were parenterally administered from this time to her death. Streptomycin, 1 gm. daily, was started on Dec. 22 and continued until her death, on Jan. 9.

She continued to deteriorate. Abdominal distention required the passage of a Miller-Abbott tube; episodes of respiratory obstruction necessitated a tracheotomy and subsequent frequent bronchoscopic aspirations; hypotension was relieved by continuous arterenol (nor-Adrenalin) intravenous infusion.

By Dec. 24 she began to improve and regained consciousness. The arterenol and intestinal suction were discontinued, but the intravenous administration of fluid and the antibiotics were continued. The urine output was satisfactory, and the urinalysis showed no pathological changes except "yeast cells" in the sediment. The temperature remained elevated.

Early in January the patient became listless and pale. There was gross melena. The hemoglobin and hematocrit levels dropped to 8.6 gm. per 100 ml. and 28%, respectively, and she was transfused with 1,200 ml. of blood. Her temperature rose to 105 F. She deteriorated rapidly and died on Jan. 9. The clinical diagnosis was acute bulbar poliomyelitis complicated by unexplained gastrointestinal hemorrhage. The day after death a blood culture taken three days previously showed a pure culture of Candida albicans.

Autopsy.—Postmortem examination confirmed the clinical diagnosis of acute poliomyelitis involving cord, medulla, pons, substantia nigra, and hypothalamus. The lungs showed marked hemorrhagic edema, with areas of atelectasis.

In the first part of the duodenum there were two kissing ulcers. The one on the posterior wall had penetrated into the pancreas and had an eroded vessel in the base. Microscopically these showed the typical structure of benign chronic peptic ulcerations. The lower intestine contained tarry stools.

The left shoulder area was markedly swollen. The intravenous injections had been into this arm. The veins were dissected, and a small thrombus was found attached to the wall of the subclavian vein. Histological examination of the thrombus and vein wall showed no organisms.

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* References 1-4.

† References 4-9.

‡ References 10-17.

Both kidneys were enlarged, weighing 280 and 300 gm. The cut surface showed numerous yellow abscesses measuring approximately 0.1 to 0.2 cm. in diameter, scattered through the cortex as well as the medulla. Microscopically these abscesses consisted of collections of polynuclear and mononuclear cells. Sections stained according to the periodic acid-Schiff method showed septal branching hyphae and budding spores to be present in several of these abscesses (Fig. 1). Similar abscesses were found in the heart muscle, peripheral muscle, and central nervous system.

Bacteriological Investigations.—Blood of this patient was added to trypticase soy broth. Subcultures were made on blood agar and Sabouraud's glucose agar. Medium-sized dull gray colonies were observed in the former, and the latter showed creamy white colonies with a distinct yeast-like odor. The organisms isolated from these plates were Gram-positive oval budding cells.

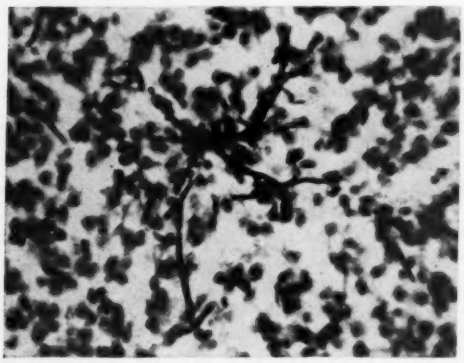


Fig. 1.—Kidney abscess with branching hyphae. Periodic acid-Schiff stain; × 300.

Subcultures were made on corn meal agar, on which medium the organism showed formation of chlamydospores. A saline suspension of the organism was intravenously injected into rabbits. These animals died within four days; at autopsy there were multiple abscesses in the kidneys, from which the organism was again isolated.

At postmortem examination swabs were taken from the kidneys, the spleen, and the lungs. These were cultured on blood agar and Sabouraud's glucose agar. The lung cultures were negative, but positive cultures were obtained from kidney and spleen. These were identified in the same way as outlined above, with the same results.

Diagnostic Conclusions.—1. Acute poliomyelitis involving the cord, the medula, the pons, the substantia nigra and the hypothalamus.

2. Bilateral pulmonary edema and segmental atelectasis.

3. Penetrating chronic peptic duodenal ulcer with hemorrhage.

4. Septicopyemia due to C. albicans, with localization in the kidneys, the myocardium, the peripheral muscles, and the brain.

5. Thrombosis of the left subclavian vein.

CASE 2.—Miss I. T., a 49-year-old woman, was admitted to the tuberculosis division on July 25, 1951, in an extremely debilitated state, suffering from far-advanced active pulmonary tuberculosis. This was discovered while she was in a general hospital recuperating from a laparotomy and temporary ileostomy performed for a bowel obstruction.

Physical examination revealed a wasted, sallow, seriously ill patient. Chest movements were restricted on the left, and there was dullness, with diminished breath sounds and scattered rales. There were several sinuses in the anterior abdominal wall discharging purulent material. The abdomen was diffusely tender. Pressure sores were present over the hips and sacrum. The fingers showed marked clubbing. The blood pressure was 135/80; hemoglobin, 10 gm. per 100 ml.; sedimentation rate, 90 mm. in an hour (Westergren). Ziehl-Neelsen stain on sputum showed numerous acid-fast bacilli.

The patient was given specific antituberculosis chemotherapy. Although there was some symptomatic improvement, with healing of her abdominal sinuses and pressure sores, there was little other change in her physical state. She continued to run a low-grade fever; her sputum remained persistently positive, and serial roentgenograms of her chest showed her pulmonary tuberculosis to be slowly progressing.

On May 7, 1953, the patient began to complain of severe hypogastric cramps with nausea and vomiting. Her stools became loose, foul, and frequent. Examination of the abdomen revealed some distention and tenderness in the right lower quadrant.

A flat plate of the abdomen revealed considerable gaseous distention of the large bowel. She was considered to have either a malignant or an inflammatory obstruction of the colon in the region of the rectosigmoid junction or a tuberculous enterocolitis. Intravenous fluids and chlortetracycline (Aureomycin) were administered. There was some temporary improvement, but she began to deteriorate again and by June 3, 1953, became semicomatose and developed a moderate degree of anasarca and scattered purpuric spots over her body. Plasma protein estimation was as follows: total, 4.07 gm. per 100 ml.; albumin, 1.30 gm. per 100 ml.; globulin, 2.77 gm. per 100 ml. Her condition rapidly worsened, and she died on June 6, 1953.

Final clinical diagnosis was far-advanced bilateral pulmonary tuberculosis with tuberculous enteritis.

Postmortem Examination.—This showed extensive chronic bilateral pulmonary tuberculosis with cavity formation in left upper lobe.

The mucosa of the ascending and transverse colon showed numerous confluent ulcers. Between the ulcers, islands of mucosa with the appearance of polyps were seen. Sections of the ulcers showed a chronic nonspecific inflammatory reaction, with marked fibroblastic proliferation.

The liver weighed 1,400 gm. and had a slightly granular pale brown surface. The cut surface was extremely pale; the acinar structure was replaced by a pattern of pale yellow raised areas surrounded by darker depressed areas. Histological examination showed proliferating fibrous tissue around the portal spaces, extending irregularly between the hepatic cells. There was also a fairly marked proliferation of the bile ducts, and there were fatty changes in the liver cells.

The somewhat enlarged and firm spleen weighed 250 gm. The cut surface showed slightly raised dark purple areas on a pale background. Sections stained with Congo red showed focal deposition of amyloid, mainly localized in the follicles.

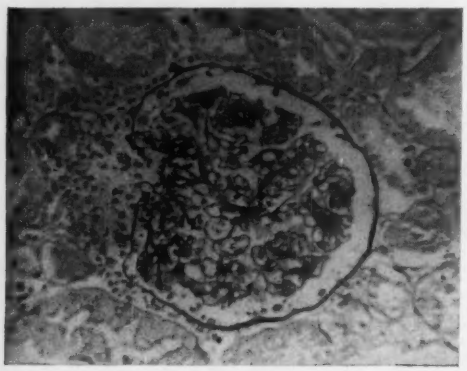
Both kidneys were large, weighing 210 and 220 gm. The cortex as well as the medulla showed numerous small pale yellow abscesses. Microscopically these consisted of collections of polynuclear and mononuclear cells. Periodic acid-Schiff stains of these lesions showed branching hyphae arranged in a somewhat radial fashion. The size of the threads varied; localized swellings were present along the course of some of them. In some lesions yeast-like budding forms were observed. A cellular reaction in connection with these hyphae was not always present (Fig. 2). Similar lesions were found in the heart muscle (Fig. 3) and in the adrenals.

Diagnostic Conclusions.—1. Chronic bilateral pulmonary tuberculosis with cavitation.

2. Chronic ulcerative colitis.

3. Early cirrhosis with fatty metamorphosis of the liver.

Fig. 2.—Kidney with branching and budding hyphae in the glomerulus; no cellular reaction. Periodic acid-Schiff stain; × 215.



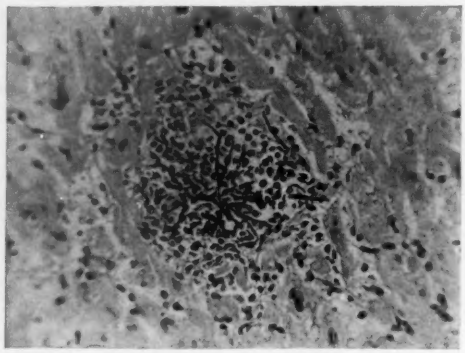


Fig. 3.—Small abscess in the heart muscle, with branching hyphae. Periodic acid-Schiff stain; × 215.

4. Generalized candidiasis with multiple abscesses in the kidneys, the heart muscle, and the adrenals.

5. Amyloidosis of the spleen.

Case 3.—Mr. E. G., age 24, was admitted on Dec. 17, 1952, with the typical signs and symptoms of acute poliomyelitis. During the day of admission he developed extensive paralysis of arms, legs, and respiratory muscles. Respirator treatment was required. He ran a very stormy clinical course, with continued fever, delirium, and episodes of hypotension for several weeks.

Intravenous administration of fluids with an indwelling polyethylene catheter was started on the third day and was continued for three weeks.

Sulfamethylthiadiazole (Thiosulfil), 2 gm. daily; the hydriodide of the diethylaminoethyl ester of penicillin G (Estopen), 500,000 units daily, and oxytetracycline, 750 mg. daily, were given for three weeks. After that streptomycin, 1 gm. daily, was given for nine days because of continued high fever and evidence of pyuria.

By the middle of January the patient's delirium had subsided but his temperature was still elevated, ranging daily from 98 to 100 F. This continued until the end of January.

On Jan. 8 urine analysis revealed many bacteria and yeast cells. On Jan. 5 and Jan. 7 blood samples were taken for culture. Yeast was isolated and was later identified as C. albicans. Antibiotic therapy was stopped and sulfathiazol was given in high dosage for five days, without apparent effect. On Jan. 16 undecylenic acid therapy was started; 15 gm. daily by mouth was given for six days, with no apparent effect. On Jan. 24 cycloheximide (Acti-Dione) therapy was started at a daily dose of 40 mg. intramuscularly. After four days this was increased to 60 mg. per day and was continued for over two months. Blood taken for culture on Jan. 31, Feb. 8, and April 16 was sterile. However, C. albicans has been isolated from catheter urine on repeated occasions up to the present time.

The patient's general condition improved slowly; his hemoglobin was within normal limits on the three occasions it was examined. However, a 48-hour urine concentration test revealed appreciable loss in renal function; the highest specific gravity achieved was 1.015. Intravenous pyelograms were reported as normal.

In March, 1953, the patient's blood pressure began to rise. Since then systolic blood pressure has been over 130 and diastolic pressure constantly over 100.

At the present time, June, 1954, although the patient still has severe residual paralysis his general health is good. His moderate hypertension is asymptomatic, as is his chronic Candida urinary tract infection. He has recently had a course of intravenous stilbamidine without effect on his pyuria.

Bacteriological Investigations.—Blood of the patient was added to trypticase soy broth. After three days the cultures showed growth. As in Case 1, subcultures were made on blood agar and Sabouraud's glucose agar. On the former, medium-sized dull gray colonies were observed; on the latter, the colonies were creamy white and had a distinct yeast-like odor. Smears from these colonies showed Gram-positive oval budding cells.

To differentiate these from other species within this group of organisms two procedures were followed. Subcultures were made on corn meal agar, on which medium the organism showed formation of chlamydospores. A saline suspension of the organism was intravenously injected into rabbits. These rabbits died within four days; at autopsy there were multiple abscesses in the kidneys, from which the organism was again isolated.

Urine samples were investigated in the same way. Primary cultures were made on glucose agar and Sabouraud's agar. The same organism was isolated.

Also, blood agglutinations were done. Positive results were obtained in a dilution of 1 : 256.

Diagnostic Conclusion. — Extensive bulbospinal poliomyelitis complicated by C. albicans septicemia, resulting in chronic pyuria.

COMMENT

The clinical importance of the recovery of Candida from human material is still a problem. In many cases of so-called bronchopulmonary candidiasis the actual importance of the fungus may be debated. The same is true in those patients whose diarrhea after long-standing antibiotic therapy is attributed to Candida infection of the intestinal tract. Wegmann [18] found Candida to be present in 10% of the material collected from pharynx, colon, and vagina in normal persons. Skinner [1] found even a higher incidence; 15% of the feces samples and 20% of the sputum samples collected from normal people contained Candida. Haley and McCabe [19] found Candida in the tracheobronchial system in 9 out of 73 successive postmortem examinations. On the other hand, there can be no doubt as to the importance of the organism in oral and vaginal thrush, the anorectal syndrome described by Manheim [20] after antibiotic therapy, and Candida infections of skin and finger nails.[2] The same is true for those rare cases of endocarditis and meningitis in which Candida was isolated from the lesions found after death. In the three cases described in this paper the presence of the organism in the blood during life and in the abscesses of several organs after death indicates that in these patients Candida was the etiological agent of the disease process.

Under what circumstances can this organism, usually showing such a low grade of virulence, become pathogenic in the human body? If we review our three cases it is quite obvious that they had several factors in common. All three patients were in extremely poor general condition at the time they developed their infection. All three had extensive antibiotic therapy and had been maintained only on parenteral fluids for a considerable time.

In 1869 Trousseau described thrush as "the local expression of a very bad state of the whole system." Lederer and Todd,[4] as well as Duhig and Mead,[8] stress the poor condition of their patients. Lederer found it was more frequent in bottle-fed babies than in breast-fed ones. The reported cases of generalized candidasis, mycotic endocarditis, and meningitis all occurred in patients in a poor state of general health. Nearly all of them were in such poor condition that they died shortly after the first symptoms of the infections appeared.

There is no doubt that the increasing number of patients with Candida infections is related to the extensive use of antibiotics during recent years [21]; however, some pathological changes occurring during antibiotic therapy are too readily ascribed to candidiasis. As Goslings [22] suggested, we should consider

whether the disease is directly due to the antibiotics or to diminished vitamin synthesis due to a disappearing normal bacterial flora or to other causes so far unknown. Zimmerman [23] stresses in his paper the importance of bone-marrow-depressing drugs and refers to observations by Farber, who found disseminated candidiasis in children with acute leukemia treated with these drugs. It is difficult in these cases to assess the relative importance of general debility as opposed to a specific depression of the cellular mechanism by the drug in question.

Duhig and Mead [8] described four cases of generalized candidiasis in infants suffering from enterocolitis, all of whom had intravenous dextrose therapy. As in our cases, intravenous therapy was given for a long time. We considered the possibility that infection was due to contaminated solutions or poor sterilization of the polyethylene tubes. Bacteriological investigation of solutions and tubes, however, did not support this contention.

As far as we are aware, our third patient and the one described by Wessler and Browne [6] are the only ones from whom the organism was isolated from the blood and who were still alive at the time of publication. Our patient is disabled by his poliomyelitis, but his general condition is good. However, he has still a chronic pyuria, Candida being the only organism isolated from catheterized urine. This indicates that Candida may be one of the organisms causing chronic pyuria if the clinical history indicates a period of lowered general resistance in the immediate past.

SUMMARY AND CONCLUSIONS

Three cases of disseminated candidiasis are reported. In two patients Candida albicans was isolated from the blood during life. One of the two survived the acute infection and is left with a chronic pyuria due to this organism.

Candidiasis is a clinical and pathological entity, decreased general resistance being the most important factor in its development.

With awareness of this possibility and by use of the right diagnostic procedures during life and after death, candidiasis will probably be found to be a less uncommon condition than one would expect from the number of cases reported in the literature.

Miss S. Campbell and Miss K. Nagy gave technical assistance.

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SYSTEMIC MONILIASIS AND ASPERGILLOSIS COMPLICATING CORTICOTROPIN THERAPY

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ALTHOUGH there have been numerous reports * of systemic fungus infection following antibiotic therapy, there have been few in the literature of a systemic fungous infection complicating corticotropin therapy. Soffer and co-workers [5] described a fatal case of lupus erythematosus with extensive pulmonary fungus infection during cortisone treatment. Antopol and Quittner [6] described a fatal case of Hodgkin's disease with diffuse bronchopneumonia produced by Aspergillis niger during therapy with both cortisone and corticotropin (ACTH). Reynell, Martin, and Beard [7] described a fatal case of peritoneal moniliasis complicating a perforated peptic ulcer following corticotropin therapy. The case presented here is another incident of systemic fungus disease following the use of corticotropin.

REPORT OF A CASE

A 24-year-old white woman, whose first of four admissions to another hospital was on May 21, 1953, was seen because of anemia and bleeding gums of three to four months' duration. One week prior to this admission the patient complained of headaches, weakness, shortness of breath, dizziness, and blurring of vision. On April 20, 1953, the patient had a dilatation and curettage for menometrorrhagia of three months' duration. She required three blood transfusions at this time. Following this procedure no further menstrual abnormalities were noted.

On admission she appeared markedly pale. A left retinal hemorrhage was present, as well as an ecchymotic area on the lateral aspect of her right knee. Her hemoglobin was 4.1 gm.; red cell count, 1,970,000; white cell count, 6,250; sedimentation rate, 70 mm. in an hour; hematocrit level, 21%, and platelets, 70,000. The differential white cell count was normal. Despite six blood transfusions, her hemoglobin did not rise, and so she was placed on corticotropin, 25 mg. intramuscularly for two doses, and was then discharged on a similar daily dose.

Her second hospital admission, two months later, was on July 15, 1953. She had had two normal menstrual periods in the intervening time. Her headaches had persisted. The hemogram revealed the red cell count to be 2,000,000; hemoglobin, 5 gm.; white cell count, 4,300, with 85% polymorphonuclear cells, 14% lymphocytes, and 1% monocytes. The serum was yellow. A bone marrow study disclosed marked increase in cellularity, with a decreased number of megakaryocytes. The bone marrow red cell-white cell ratio was 1:12, with a shift to the left of the white cell series; 50% of the cells were blasts. The diagnosis of acute blastic leukemia was made. The patient was given three transfusions, and her hemoglobin rose to 9.5 gm. She was discharged on corticotropin, 40 units intramuscularly, daily.

The third admission was on July 27, 1953, because of epigastric distress, nausea, and swelling of the ankles. Her sclerae were icteric, and her skin was yellow. There was no

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* References 1-4.

hepatic tenderness. Prothrombin time was 35%; hemoglobin, 9.5 gm.; red cell count, 3,200,000; white cell count, 8,100; differential count, normal. Twenty-five milligrams of corticotropin was given intramuscularly every six hours from July 27, 1953, to July 30, 1953, on which day the patient was discharged on the same daily dosage.

Her fourth admission was from Aug. 13, 1953, to Aug. 21, 1953. At this admission an abscess was noted on the flexor surface of the right fourth finger. She disclosed that she had cut herself with a razor blade in this area two weeks previously. She still complained of headaches, The oral temperature was 103.0 F. A discrete papular rash was present over the face, arms, chest, and back. There was a diffuse cloudy white membrane over the soft palate, which did not strip. A Grade II systolic murmur was present to the left of the sternum in the third and fourth costal interspaces. Several purpuric areas were present on the lower extremities. On August 13, 1953, the abscess on the finger was incised. Cultures revealed hemolytic Staphylococcus. On Aug. 14, 1953, the patient experienced a grand mal seizure. Therapy during this admission was as follows: from Aug. 13 to 17, penicillin, 600,000 units a day; from Aug. 17 to 19, topical polymyxin B applied to the finger lesion; from Aug. 19 to 20, sulfadiazine, 4 gm. daily; from Aug. 20 to 25, corticotropin, 40 units daily. The cephalin-cholesterol flocculation was 3+ in 24 hours and 4+ in 48 hours. Hemoglobin during this admission ranged from 5.5 gm. on admission to 13 gm. after five whole blood transfusions. The white cell count was 8,000, with 80% neutrophiles. Hypochromia, poikilocytosis, and anisocytosis were noted.

Final Hospital Admission.—On Aug. 28, 1953, the patient was transferred to the medical service of Michael Reese Hospital. She appeared acutely ill, lethargic, and confused. Her blood pressure was 106/70; pulse rate, 110; temperature, 101.0 F. There was a brown maculopapular eruption over the face, chest, and arms. The sclerae were icteric. The right and left optic disc margins were blurred. A white plaque was seen on the right tympanic membrane. Similar plaques were seen on the buccal mucosa and tongue. The thyroid was slightly enlarged. Small lymph nodes were palpable in the cervical and auxiliary regions. Examination of the chest revealed decreased breath sounds and dullness to percussion in the right lower lobe posteriorly. The heart was not enlarged. There was a Grade II systolic murmur over the second left interspace. The liver and spleen were just palpable. There was bilateral ankle clonus and a positive left Oppenheim sign. There was an area of redness and desquamation on the flexor surface of the right fourth finger.

A round firm pea-sized lesion was excised from the subcutaneous tissue of the scalp.

Laboratory Data.—Hemoglobin, 12.6 gm.; red cell count, 4,200,000; white cell count, 10,400; segmented polymorphonuclear cells, 66%; nonsegmented polymorphonuclear cells, 10%; lymphocytes, 20%; monocytes, 4%; reticulocytes, 0.8%; hematocrit level, 41; color index, 0.97; sedimentation rate, 40 mm. in an hour. Urinalysis revealed 3 red cells, 5 white cells, and 4 cellular casts per high-power field. Bone marrow examination revealed hypoplasia of the red cell series, hyperplasia of the white cell series, and no evidence of leukemia. The liver profile was normal except for albumin of 2.5 gm. and globulin of 3.5 gm. A spinal fluid examination on Sept. 22, 1953, revealed the fluid to be clear and colorless, with 23 fresh red cells and 9 white cells, consisting of 6 polymorphonucelar cells and 3 lymphocytes; glucose, 54 mg. per 100 cc.; protein, 68 mg. per 100 cc., and chlorides 655 mg. per 100 cc. Chest x-ray revealed a diffuse mottled infiltrate throughout both lung fields. The electrocardiogram was suggestive of myocarditis and pericarditis. Candida albicans was cultured from lesions of the scalp, tongue, and throat. The urine revealed both Aspergillus and C. albicans. The blood cultures and spinal fluid culture were negative.

Course.—The optic discs became more blurred. A lumbar puncture on Sept. 21, 1953, revealed a pressure of 300 mm. of water. On Sept. 22, 1953, the patient suddenly became apneic, cyanotic, and atonic, with a slowing of the pulse from 100 to 70. She recovered from this episode after oxygen inhalation. A similar episode, again relieved after oxygen therapy, occurred two hours later.

Treatment during this admission included benzathine penicillin G (Bicillin), 600,000 units daily, for the first 10 days. On Sept. 24, 1953, the patient was given potassium iodide and intravenous methylrosaniline chloride (gentian violet) therapy. On Sept. 26, 1953, she developed slight nuchal rigidity and later became comatose. On Sept. 28, 1953, the patient died.

Postmortem Pathology.—Postmortem findings revealed generalized abscesses due to infection with Aspergillus and C. albicans, affecting particularly the heart and pericardium, the lungs and pleura, brain, dura mater, liver, spleen, kidneys, right suprarenal, the left lobe of the thyroid, peritoneum, and skin.

Fig. 1.—The surface of both kidneys was studded with yellow nodules. On section, some of them were seen to have penetrated into the medulla.

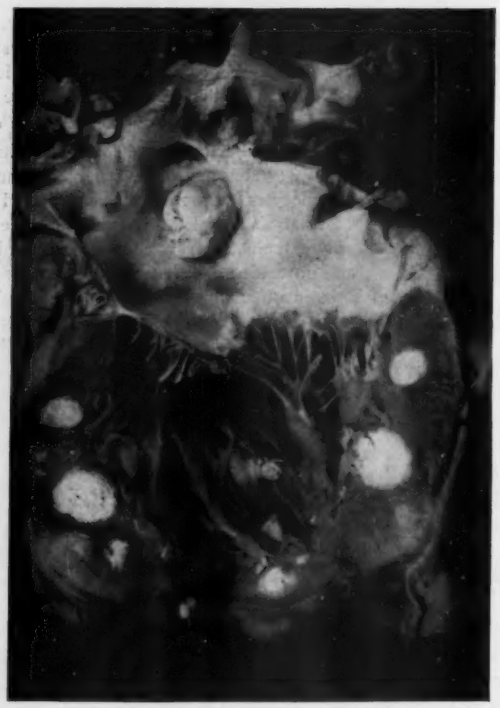

Fig. 2.—Yellow nodules were found on the pericardium, penetrating through the myocardium and into the endocardium. A large polypoid mass was seen in the fossa ovalis, made up of material similar to that found in the nodules.

The bone marrow and lymph nodes showed no evidence of leukemic infiltration.

Microbiologic Study.—Specimens from the various abscesses were cultured on Sabouraud's media at 37 cc. and were subcultured on Sabouraud's slants. Other specimens (heart, brain) were placed in beef heart infusion agar with streptomycin and penicillin at 37 C.

For bacteriological study, 0.1 cc. of the specimen was inoculated on Brewer's thioglycollate broth, with subcultures on blood agar and Endo's (methylene blue) plates.

C. albicans was identified by its terminal chlamydospores on corn meal agar. This was verified by sugar fermentation tests.

Aspergillus was identified by wet mounts and colonial growth. The significant postmortem bacteriological findings were as follows:

Specimen	Bacteriology	Mycology
Brain lesion	Staph. aureus (coag. pos.)	Aspergillus
Heart lesion	.....	Aspergillus
Abscess immediately posterior to trachea	Staph. aureus (coag. pos.)	Aspergillus
Lung lesion adherent to posterior chest wall	Staph. aureus (coag. pos.)	Aspergillus C. albicans
Lung, peripheral node	.....	C. albicans
Lung, parenchyma	.....	C. albicans
Intact tracheal lymph node	Staph. aureus (coag. pos.)	.....
Anterior chest wall node	Staph. aureus (coag. pos.)	C. albicans
Skin lesion, left hip	.....	C. albicans
Kidney lesion	Staph. aureus (coag. pos.) Aerobacter aerogenes Tubercle bacilli, culture	.....
Spleen lesion	Staph. aureus (coag. pos.)	C. albicans
Vagina	.....	Nonspecific yeast

COMMENT

The most important consideration in this case is an explanation of why normally localized infections such as moniliasis and aspergillosis should suddenly disseminate throughout the body, causing widespread abscesses. It has been shown experimentally that the reticuloendothelial system seems to be blocked by cortisone.† In addition, it has been stated that the unfavorable action of cortisone may be related to an interference with the mobilization of phagocytic cells [12] or to an interference with normal fibroblastic formation. It has also been demonstrated that cortisone protects an organism from an infection produced by bacterial toxin [11] but has no effect and even enhances an infection caused by non-toxin-producing organisms, whose mechanism of causing disease is by "direct spread."‡ Whether one or all of these suggested mechanisms is in effect during adrenal cortex therapy is not clear at present. However, it becomes apparent there is some profound change in the human organism which allows dissemination of infection.

As noted previously, rapidly disseminating fungus infections have been repeatedly observed in patients treated with antibiotics over a long period of time. In the absence of long-term antibiotic therapy, we have postulated that the spread of Aspergillus and Monilia in this case was due to corticotropin therapy.

The underlying cause of the anemia and thrombocytopenia, this patient's first manifestation of disease, was never demonstrated, either in vivo or after death. It was felt that the initial focus of the fungus infection may have been the mucous membrane of the mouth or the vagina or the infected finger. The finding of tubercle bacilli in the kidney at postmortem examination was thought not to be contributory to the systemic disease, as there was no other evidence for tuberculosis on gross or microscopic examination. The widespread distribution of coagulase-positive Staphylococcus aureus was thought to have been a terminal invasion rather than a primary cause of the patient's death.

† References 8-10.

‡ References 12 and 13.

SUMMARY

The case presented is that of a 23-year-old white woman, whose first manifestation of disease was a bleeding tendency. Thrombocytopenia and bone marrow characteristic of acute blastic leukemia were found. On this premise the patient was started on corticotropin therapy, which was continued for three months.

She developed evidence of systemic disease, which on postmortem examination was found to be a generalized fungus infection.

It is postulated that the dissemination was due to corticotropin therapy, and several possible mechanisms for this dissemination are suggested.

Dr. A. M. Rywlin did the postmortem examination, and Miss Helen MacLean performed the bacteriological studies.

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Treatment in Internal Medicine

TREATMENT OF CARDIAC ARRHYTHMIAS

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THERE has been a resurgence of interest in cardiac arrhythmias in the past few years. Many excellent papers have been published reporting clinical and experimental investigations of the nature and treatment of these disturbances. From this wealth of data and detail one fact emerges with startling clarity, namely, that digitalis and quinidine still retain their positions of preeminence as antiarrhythmic drugs. The work and experience of recent years have resulted in a better understanding of the action and methods of employment of these two drugs and, in addition, have brought into prominence various agents of lesser importance but of occasional great value. It is the purpose of this paper to review briefly the current status of the management of cardiac arrhythmias. A simplified list of recommended drugs and dosages is appended in the Table.

It is obvious that not all arrhythmias need to be treated. Sinus arrhythmia, sinus bradycardia, A-V nodal rhythms (including interference dissociation), and many cases of complete heart block are quite benign so far as their rates and rhythms affect the body economy, and there is little point in trying to alter them. Sinus tachycardia is not amenable to specific treatment, except in a transient way. The arrhythmias of practical importance to the physician are premature systoles, paroxysmal tachycardia, atrial flutter, atrial fibrillation, and Adams-Stokes syndrome. Possible precipitating mechanisms such as tobacco, alcohol, gastrointestinal factors, and various drugs should be recognized and corrected. The interested reader is referred to several recent publications for their content and for their useful bibliographies.*

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PREMATURE SYSTOLES

Treatment is necessary only when the patient's awareness of the arrhythmia results in apprehension or when frequent extrasystoles are associated with heart disease. Sedation with barbiturates is successful very often in the former case and occasionally in the latter. Quinidine is effective in many instances, regardless of the origin of the premature beats. In several cases I have observed a temporary increase in the frequency of extrasystoles for about one to two hours after each dose, of sufficient degree to disturb the patient. This has also occurred with procaine amide (Pronestyl). Another point which is not generally appreciated is that digitalis often abolishes premature beats even when there is no heart failure.† In fact, it has been possible to make use of this effect in studying the latent period of digitalis preparations.‡ I have been disappointed in the use of nitrites in efforts to abolish extrasystoles associated with coronary disease.

PAROXYSMAL TACHYCARDIA

Supraventricular Tachycardias.—Vagal stimulation by carotid sinus pressure, eyeball pressure, Valsalva maneuvers, or induction of the gag reflex should be tried as the initial treatment in every case. These methods are too well known to require discussion here. Various drugs may be used when simpler measures fail.

Digitalis is probably the most popular agent of choice, preferably in the form of a rapidly-acting glycoside administered parenterally. Lanatoside C works well when given

* References 1-6.

† According to Lewis,[7] "Digitalis as a direct measure is contra-indicated."

‡ References 8 and 9.

intramuscularly. By this method it appears to be about a half hour slower than after intravenous injection, with peak effects appearing in 60 to 90 minutes. Digoxin works in a similar fashion and may also be given intramuscularly. New forms of these preparations are available, and they are preferred because they are less irritating locally (see Table). The intramuscular route is safer than the intravenous route, and even greater safety can be achieved by giving fractional doses at intervals.

Quinidine is possibly as effective as digitalis, but it has several disadvantages. The effective total dose is unpredictable. Therefore the treatment may take many hours or even many days, and evidence of intolerance or toxicity may appear before the paroxysm is terminated. Procaine amide, in my experience, has proved to be distinctly inferior to quinidine in all atrial arrhythmias. Indeed, I have found quinidine by mouth to be more effective than large doses of intramuscularly administered procaine amide.

Sedatives and narcotics have an important place in the treatment. Barbiturates are often effective within a few hours, especially in patients with little or no heart disease. Morphine is particularly effective, and it deserves much wider use.

Methacholine is frequently successful, but it often produces such violent side-effects that it should be reserved for use only as a last resort. Neostigmine (Prostigmin) has been quite ineffective in my hands, even in single doses as high as 1.5 mg. intravenously. Its chief value is in enhancing vagal sensitivity so as to potentiate the effect of carotid sinus pressure or vagus-stimulating drugs.

Phenylephrine (Neo-Synephrine) is often effective, but it must not be used for hypertensive persons, since it probably acts by virtue of an abrupt pressor response which results in reflex vagal stimulation.[10] I have seen paroxysms of atrial tachycardia abolished within seconds of the intravenous injection. It acts at least as quickly as methacholine and even more rapidly than acetylstrophanthidin. However, I have noted frequent ventricular premature systoles and transient A-V block after reversion to sinus rhythm, and several patients have complained of pounding headaches and of bladder cramps following the injection. Preliminary reports on the use of methoxamine (Vasoxyl) are encouraging, since this substance appears less likely to produce ventricular arrhythmia.§ It may be that the methoxyl group exerts a specific antiarrhythmic action.[1]

Recurrences can be prevented by either digitalis or quinidine. It is difficult to know in advance which agent will be more successful in a given case. Hence the trial and error method cannot be avoided. It has been customary to continue digitalis in those cases which had been successfully treated by digitalis and to do likewise with quinidine.

Ventricular Tachycardia.—The primary objective is to reduce the frequency rather than to insist upon abolition of all ectopic ventricular activity, since the latter course may be very dangerous in the presence of myocardial infarction.‖ The agent of choice is either quinidine or procaine amide. If oral quinidine cannot be tolerated, or if greater speed of effect is desired, then intramuscular procaine amide should be used.[16] Intramuscular quinidine preparations are not uniformly absorbed and are quite irritating locally. The risk entailed in intravenous administration of either quinidine or procaine amide is great enough to outweigh the advantage of the greater speed of action and should therefore be resorted to only in the most extreme emergencies. Very slow intravenous administration of either of these drugs offers no advantage over intramuscular administration of procaine amide, since the latter may produce effects in a few minutes.

Digitalis is contraindicated except when congestive heart failure is present. Nevertheless, I have seen a case in which 0.75 mg. of ouabain was given, through a misunderstanding, and reversion to normal sinus rhythm occurred 20 minutes later. Vasopressor drugs may be necessary to maintain blood pressure, especially when procaine amide or quinidine is being used. Morphine

§ References 11 and 12.

‖ References 1, 14, and 15.

intravenously has been successful in some cases, stopping the paroxysm in a few minutes.[17] I have tried it in two cases without success.

ATRIAL FLUTTER

It cannot be emphasized too strongly that digitalis is the drug of choice and that it is often necessary to be persistent in using it in liberal doses. The best way is to give fractional doses at intervals of four to eight hours until a therapeutic effect occurs or distinct intoxication ensues. It is even possible that the conversion of flutter is actually a manifestation of some degree of digitalis toxicity. The immediate objective is to slow the ventricular rate, regardless of the atrial mechanism. When the ventricular rate is brought down to a reasonable level, digitalis dosage should be adjusted to maintain the rate. Sometimes the long-acting preparations, such as digitalis leaf or digitoxin, work more efficiently in reducing the ventricular rate than digoxin. Often enough, on such a regimen, the atrial flutter will eventually change to fibrillation and even to normal sinus rhythm without further adjustment of dosage. I have seen many patients made unnecessarily sicker by stubborn efforts to restore normal rhythm, when they could easily have been kept comfortable with a normal ventricular rate while the atria were still fluttering or fibrillating.

Quinidine is successful in about one fifth to one third of cases of flutter, chiefly in the paroxysmal variety. Its use is often attended by a rise in ventricular rate concomitant with the fall in atrial rate, the so-called paradoxical tachycardia.[18] This tachycardia frequently cannot be prevented by prior and even current use of digitalis. I have found procaine amide, even in very large doses intramuscularly, ineffective in chronic flutter.

ATRIAL FIBRILLATION

The management of chronic atrial fibrillation as ordinarily encountered in clinical practice is classic, and it needs no further elaboration here. However, an acute paroxysm of fibrillation may present problems. In many instances this arrhythmia occurs suddenly during the course of illness not associated with heart disease, and it may become a dangerous complication. Despite popular belief, digitalis is often completely ineffective in slowing the ventricular rate or in abolishing the arrhythmia, whereas quinidine may succeed quickly. An expeditious method is to give a rapidly acting digitalis glycoside parenterally.[19] If neither significant slowing nor reversion to normal occurs within an hour then quinidine treatment should be begun at once. When uncontrolled thyrotoxicosis is present this arrhythmia is usually difficult to treat, although I have seen partial slowing of the ventricular rate by digitalis in some cases and even occasional reversions after quinidine. Recurrent paroxysmal fibrillation in otherwise healthy persons usually can be abolished by quinidine or procaine amide, and recurrences can be prevented by quinidine.

The physician is often confronted with the question of whether to attempt to convert chronic fibrillation to normal rhythm. Despite the rosy figures in many reports, the fact is that only a small minority of patients are subjected to quinidine therapy. In general, conversion of fibrillation and maintenance of normal rhythm is less likely the more serious the degree of heart disease. I have been impressed by the experience that the greater the dose of quinidine required to convert the arrhythmia, the greater the likelihood of recurrence despite large maintenance doses. Repeated changes in the rhythmic mechanism are not only unsettling but also dangerous for the patient. Even after successful mitral commissurotomy it is difficult to obtain reversion in patients with advanced mitral stenosis. Quinidine therapy is indicated in patients with lesser grades of heart disease, in patients who are seriously disturbed by their awareness of the arrhythmia, and in those whose condition is difficult to control with digitalis. Procaine amide is distinctly inferior to quinidine in the conversion of chronic atrial fibrillation.

It has been taught that quinidine therapy is potentially dangerous by virtue of a possible dislodgment of mural thrombus imme-

diately consequent to the restoration of coordinated atrial contractions. This has generated a widespread fear which has become almost a medical tradition. Nevertheless, the most striking aspect of this type of embolism is its rarity, not only in general clinical experience but also in the literature, where well-substantiated case reports are very rare indeed. In some clinics it is the practice to use anticoagulant drugs prior to and during quinidine therapy. This method is actually capable of limiting accretions of fresh thrombus only and is surely no guard against the dislodgment of old thrombus. It is questionable whether the theoretical benefits from the use of anticoagulants during quinidine therapy outweigh the added inconvenience associated with their use and the possible hemorrhagic complications, except perhaps in cases of repeated embolisms in the recent past.

ADAMS-STOKES SYNDROME

The actual mechanism producing syncope is rarely apparent in a given case. It may be extreme ventricular slowing, complete cardiac standstill, ventricular standstill, ventricular tachycardia, or ventricular fibrillation. In fact, the same patient may have different mechanisms at various times. Therefore, rational treatment during the seizure is practically impossible. Injection of drugs is pointless, since the circulation is arrested. Recovery generally occurs regardless of the treatment, because most attacks are self-limited. I have seen several instances of apparently successful mechanical stimulation by striking the chest with the fist or by needle puncture of the right ventricle.[20] It is possible that an externally applied electric stimulator will provide the solution.[21]

Drug treatment is indicated in some cases of complete heart block in order to prevent Adams-Stokes attacks. Epinephrine and ephedrine are often effective, as is isopropylarterenol (Isuprel). Atropine is occasionally of value. The selection of the drug should be based on electrocardiographic observations of its effects on the patient's ventricular response, avoiding any agent which results in frequent ventricular ectopic beats. Above all, quinidine and procaine amide must be recognized as dangerous by virtue of their tendency to initiate ventricular tachycardia and ventricular fibrillation in complete heart block.¶

DIGITALIS INTOXICATION

Specific treatment is rarely necessary, since withdrawal of the digitalis preparation and discontinuance of diuretic injections is generally followed by disappearance of toxicity.[6] However, occasionally it may become mandatory to attempt specific therapy—in cases where rapid toxic arrhythmias have appeared, such as frequent multifocal ventricular premature systoles, ventricular tachycardia, atrial tachycardia with A-V block, or atrial fibrillation. The drug of choice is potassium, provided there is no significant degree of renal failure.[24] Magnesium is not of much value, because its action is too short-lived.[25] While I have used both quinidine and procaine amide with benefit in such cases, it is best to avoid these agents in digitalis intoxication, because of the theoretical danger of producing ventricular fibrillation or ventricular arrest.# Morphine may be very useful in cases which have repetitive paroxysms of arrhythmia or rapid ventricular rate during atrial fibrillation. The gastrointestinal and neurologic disturbances associated with digitalis intoxication cannot be affected directly by any drugs.

Other manifestations of digitalis toxicity, such as incomplete A-V block, sinus bradycardia, sinus arrests, A-V nodal rhythms, and interference dissociation, generally require no treatment. They are apt to become worse after potassium, but they may respond fairly well to atrophine or methantheline (Banthine).

ARRHYTHMIAS DURING ANESTHESIA, SURGERY, AND CARDIAC CATHETERIZATION

During anesthesia and surgery specific therapy of arrhythmias is usually not indicated, since most arrhythmias abate spontaneously when proper pulmonary ventilation and satisfactory blood pressure levels are

¶ References 22 and 23.

References 26 and 27.

maintained. Our experience with mitral commissurotomy at Montefiore Hospital indicates that specific drug therapy is not required in most cases, even when episodes of ventricular tachycardia are present.[28] Antiarrhythmic drugs are disappointing when used to prevent arrhythmias during cardiac catheterization and cardiac surgery. Apparently they fail completely to stifle the effect of mechanical stimulation of the heart.[29] Drug action in the anesthetized patient is often strikingly different from that in the unanesthetized. For example, neostigmine in small doses may result in marked slowing of the ventricular rate during anesthesia and atropine in small doses may result in sinus tachycardia of significant degree.

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List of Recommended Cardiac Drugs for Treatment of Arrhythmias

Drugs	Indication	Dosage and Method of Use
Digitalis leaf	Atrial flutter; atrial fibrillation with rapid ventricular rate; premature systoles not due to digitalis	0.4 gm. every 6 hr. until therapeutic effect; maintain on 0.1-0.2 gm. daily
Digitoxin		0.6 mg.; then 0.4 mg. every 6 hr. until therapeutic effect; maintain on 0.05-0.2 mg. daily
Digoxin		1.0 mg.; then 0.5 mg. every 6 hr. until therapeutic effect; maintain on 0.25-0.75 mg. daily
Lanatoside C (Cedilanid)	Atrial tachycardia; urgent cases of flutter and fibrillation	1.6 mg., preferably in 2 doses about 4 hr. apart, and preferably by intramuscular route; maintain with oral preparation, as above or, if oral preparation cannot be tolerated, 0.2-0.4 mg. daily
Desacetyl lanatoside C (Cedilanid D)		
Digoxin solution (new formulation in propylene glycol)	Atrial tachycardia; urgent cases of flutter and fibrillation	Same as lanatoside C
Quinidine sulfate	Premature systoles; conversion of chronic atrial fibrillation	0.2 gm. q. i. d.; increase dose by 0.1 or 0.2 gm. every 3 or 4 days until therapeutic effect or toxicity; maintain on about half of last dosage level
	Ventricular tachycardia; urgent cases of atrial fibrillation	0.2 gm. every 2 hr. for 5 successive doses; increase dose by 0.1-0.2 gm. after 1 or 2 days
Procaine amide (Pronestyl), 10% solution	Ventricular tachycardia; urgent cases of atrial fibrillation	0.5-2.0 gm. intramuscularly, depending upon urgency; subsequent doses 0.5-1.0 gm. at intervals of 1 to 6 hr.
Procaine amide	Same as for quinidine by mouth	As substitute for quinidine in cases of intolerance, use doses 3-4 times as large as would have been used for quinidine
Phenylephrine (Neo-Synephrine)	Atrial and nodal tachycardia, only in absence of hypertension	0.4 mg. intravenously; if no effect, after blood pressure returns to preinjection level (about 15 min.), double dose and repeat this method; further increments must be added cautiously; patient should empty bladder before treatment
Methoxamine (Vasoxyl)	Atrial and nodal tachycardia, only in absence of hypertension	5-10 mg. intravenously
Neostigmine (Prostigmin)	Atrial and nodal tachycardia	0.5 mg. intramuscularly; best for potentiating carotid sinus reflex
Atropine sulfate	Complete heart block; Adams-Stokes attacks	1-2 mg. intravenously for testing response; oral doses of 1 mg. t. i. d. if successful
Epinephrine	Complete heart block; Adams-Stokes attacks	0.25-1.0 mg. subcutaneously (deep) for testing response; later doses depending upon response
Ephedrine sulfate		30-45 mg. by mouth, to test response; if successful, 15-30 mg. t. i. d.
Isopropylarterenol (Isuprel)		0.2 mg. intravenously for testing response; if successful, 15 mg. sublingually every 2-5 hr.
Potassium chloride	Serious digitalis toxic rhythms (multifocal ventricular ectopic beats; ventricular tachycardia; atrial tachycardia with A-V block)	Single dose 5-7.5 gm.; if good effect in an hour, repeat doses 2-4 gm. every 6-8 hr.; in urgent cases, 40 mEq. KCl in 500 cc. 5% dextrose intravenously per hour up to total of 120 mEq. maximum (preferably less)
Magnesium sulfate		20 cc. of 20% solution rapidly injected intravenously; good only for quick temporary effect

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Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY

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IN A REMARKABLY useful book on the frontal areas of the human cerebral cortex, Greenblatt and Solomon have edited and assembled the work of a notable team of 53 research workers at the Boston Psychopathic Hospital. The title of the book is "Frontal Lobes and Schizophrenia," [1] but the scope of the work is broader than "schizophrenia" would imply. The comparative anatomy and physiology of the frontal areas are discussed, and pertinent animal experiments are described. A brief review is given of former work on the frontal areas of man both at the Boston Psychopathic Hospital and elsewhere. Then a detailed description is given of the methods applied to the 116 cases included in the present study. It is the breadth of view and variety of investigative approaches that make this study unique. Other authors, like Rylander, have carefully followed up their postlobotomy patients and have considered social and family reports as important. Greenblatt and Solomon took into their team sociometrists, sociologists, and social workers and made careful qualitative and quantitative evaluations of the patients' behavior before and after operation. For example, a time-sampling method was devised by which the patients' behavior as a group member was observed and scored for periods of 46 minutes, twice before operation, and after operation at one month, four months, and nine months. They show that quantifying describable social behavior on a time-sampling basis can transform empirical observation into a significant research instrument. Clinical impressions are valuable, but much more open to bias than these carefully scored observations. The occupational therapy room was transformed into a laboratory, not by changing the work and treatment of the patients but by adding to the number of workers, so that the behavior of these especial patients could be accurately described and scored. Even the patients judged to be "unimproved" by operation showed changes of a favorable nature, which were missed in the more orthodox clinical and psychological examinations.

The psychological battery of tests was unique and was skillfully adapted to the problem. Physiological observations were extensive and ingenious. The "polygraph" observations on 26 of the patients are important. A drop in heart rate, face temperature, and sweating was regularly observed after operation; this is associated with decreased anxiety. The data suggest that psychotic patients whose physiological characteristics resemble a reaction to epinephrine are more likely to recover than those whose reaction resembles that seen after injection of arterenol (nor-Adrenalin).* The pathology of leucotomy is described by giving the findings in 15 cases in which the patients died.

No better summary can be made of the results than that given by the authors, on page 412:

> Leukotomy produces its effects by causing great reduction in cells and circuits in the frontal lobes. Thus impulse energy and temporal delay are decreased. Several necessary changes stem from this primary reduction: (1) The patient loses drive,

* The terminology is confused. Some authors use the terms Adrenalin and nor-Adrenalin; others say epinephrine and norepinephrine. I prefer epinephrine and nor-Adrenalin, for their auditory contrast. [Editor's note: The A. M. A. Press requires that the terminology for drugs accepted by the United States Pharmacopeia, the National Formulary, and the Council on Pharmacy and Chemistry be used in its publications. Therefore, epinephrine and arterenol have been used in this instance.]

force, energy. (2) He is less affected by past experience and more bound to immediate stimuli. (3) He is less able to elaborate experiences and less able to sustain experiences.

In comparing psychotic period (preoperatively) with postoperative period, the losses are seen mostly as a reduction in emotional tension, anxiety, fear, worry, hostility and the like. Frontal lobe circuits are therefore conceived of as the mechanism sustaining emotional tension in psychotic individuals. The loss of tension in psychotic patients is a definite gain, for sustained tension causes a disorganization in their powers of social adaptation.

With a reduction of emotional tension, psychotic individuals show a great unblocking or release of health functions. They are better organized, more capable of abstract thinking, more friendly, more social and more productive.

Unilateral frontal lobe operation may fail to produce satisfactory results because emotional tension is only partially relieved. Operations which sacrifice an excess of tissue, such as full bilateral lobotomy, may give less than optimal results because initiative is impaired or emotional capacity lowered to unsatisfactory extent. The bimedial lobotomy lowers emotional tension without sacrificing unduly either initiative or emotional response. Bimedial lobotomy appears to give the best overall clinical results of the several operations with which we have had experiences.

EPILEPSY AND CEREBRAL PHYSIOLOGY

Hippocrates began the scientific study of epilepsy, referring it to the brain. If his method of observation and deduction could have been followed, medicine would have been spared a lag of over a thousand years. But European man was not ready for the scientific method; his thinking was still animistic and supernatural. One has to take the long journey to Fernel and Paracelsus in the 15th century before dogmas are cast off and some measure of objectivity achieved. Then another groping period of 400 years intervenes before Jackson and Gowers in the 1880's studied epilepsy as keen clinicians; they saw clearly that its phenomenology gives much insight into the physiology and anatomy of the brain. An astonishing number of Jackson's theories have been verified by modern methods.

The modern era in the study of epilepsy began with three great advances. First, the neurosurgical technique, allowing craniotomy under local anesthesia with exploration of the brain of a conscious patient; second, electroencephalography; third, the development of new anticonvulsant drugs. Penfield and Jasper have been pioneers in this period of 30 years of rapid gain in knowledge. Their book "Epilepsy and the Functional Anatomy of the Human Brain"[2] is indeed epoch-making; it contains 896 pages of well-documented and beautifully illustrated observation and discussion; it tells the story of their own monumental work and of the whole period. They conclude with this paragraph, that shows them to be fine physicians as well as eminent investigators:

Throughout the analysis of every case, the clinician should be, first and foremost, a wise physician and an understanding friend to the patient. He should weigh for him the chances of success by surgery and balance this against the best that conservative treatment can promise. He must see the whole problem in the perspective of the patient's own outlook upon life.

Penfield's great contribution comes from his ability to judge wisely, operate skillfully, and make out of each operation a carefully recorded experiment that adds to medical knowledge. On page 785 he says:

The neurosurgeon who would succeed in the cure of focal epilepsy should have some interest in neuropathology and neurophysiology. He must have a stout heart as well as a trained hand, for he must be patient during long, tiresome procedures under local anesthesia. But the rewards are great, for in no other field of medicine are patients more grateful for success, and in no other field is the gradually unfolding story of neurophysiology more exciting.

A chapter by Francis McNaughton summarizes medical treatment in 28 pages. He tells of the new drugs, the management of epileptic patients, and advice to the family. There are other special chapters on cranial roentgenography, electroencephalography, and surgical therapy. The main body of the book describes in detail, with clinical examples and electroencephalographic and pathological data, the phenomena of epilepsy and the manifold ways in which these phenomena give one insight into the workings of the brain.

Throughout the discussion of anatomy and physiology one finds reference to the "centrencephalic system." This is an intriguing but debatable concept, which I discuss below in relation to the Laurentian Symposium. The evidence is clear as given by Penfield and Jasper for the presence of neurone systems from diencephalon to most parts of the cortex and back. They practically ignore the intracortical association tracts.

If this were a textbook on epilepsy one would expect more about the treatment of the nonsurgical cases, more on psychology, and certainly a chapter on genetics. But this book is largely a report of the author's own experiences and theories and as such is well conceived and beautifully produced.

RETICULAR FORMATION

In 1953 the activating mechanisms of the brain stem were discussed in this review [3] and "consciousness" was defined, at least as it applies to medicine. The basic work of Ranson, Hess, and Magoun was reviewed. Magoun and his associates,† especially, have thrown new light on this controversial subject. They have shown that there lies in the reticular formation of the brain stem an activating system, stimulation of which arouses an animal to alertness. It also changes the electrocortical activity from the more synchronized sleep patterns to the lower-voltage, more rapid wave patterns of wakeful activity.

Since this subject is so important and under such active investigation, it seems appropriate to report on the symposium held in Canada in August, 1953.[8] Magoun opened the meeting with an account of his experiments on the reticular system of the upper brain stem, showing what an important part it plays in the maintenance of awareness. Alszewski, from the Montreal Neurological Institute, followed with a discussion of the cytology of the area. He considers the term "reticular formation" too vague and prefers to call it the "central internuncial system." This is a good name, because it indicates the nature of the mechanism, i. e., a mass of neurones interposed between the well-known long tracts and the diffuse intralaminar nuclei of the thalamus. Impulses are received by way of collaterals arising from the long classic tracts and ending in the reticular formation, where several relays carry them diffusely to the thalamus. A thalamocortical system then takes them on to widespread distribution in the cerebral cortex. The cerebellar influence on this system was shown by Morrizzi (Pisa, Italy). Ingvar (Sweden) showed that slow effects occur even when neuronal connections to the cortex are severed, proving that vascular and humoral mechanisms are important.

Jasper's (Montreal) work with microelectrodes shows that there is a distribution to the cortex for this "internuncial" or "reticular" system which is different from that of the specific afferent tracts. It is widespread and nonspecific. It seems to have a general effect upon the cortex and to have nothing to do with the highly specialized, discriminative function of the classic sensory receiving stations of the neocortex. The great specific afferent tracts are spinal and bulbar somatic, cerebellar, auditory, visual, and olfactory. All of these tracts have relays in specific nuclei in the ventral part of the thalamus (except the olfactory, which goes directly to the hypothalamus). They also send off collateral branches to the reticular formation of the upper brain stem for the "unspecific" function carried out by the diffuse thalamocortical projection systems, which have their cells of origin in the mesial parts of the thalamus. The general function of these nonspecific projections is probably closely related to awareness of environment, alertness, and similar functions usually loosely grouped under the term "consciousness." At least the degree of anesthesia used on the experimental animals is of critical importance.

Brazier (Boston) reported observations made with electrodes implanted in a human brain. She also showed that careful manipulation of barbiturate anesthetic level in animals can bring out three different kinds of cortical

† References 4-7.

response, which may be associated with the long direct tract, the reticular system, and a secondary discharge. She postulates an inhibitory mechanism in the brain stem affecting the indirect "internuncial" or "reticular" system. This inhibition seems to be removed by certain levels of barbiturate anesthesia. Bremer (Belgium) discussed his preparations of cats with isolated brain. They sleep because no impulses come from below to arouse them. Especially important are those which come from the caudal part of the reticular formation of the mesial brain stem and have been cut off by this operation. Such cats can only be aroused by cortical stimulation, which he equates with "attention."

Adrian (Cambridge, England), on the basis of his vast experience in sensory physiology and especially his recent experience on the olfactory bulb, suggested the hypothesis that an editing, or selecting, function takes place in the reticular formation and that this may result in what we call "attention." This area is the meeting ground of all signals from receptor organs; the reticular mechanism might add its impulses and reinforce or withhold impulses and thus suppress specific afferents. Lashley (Harvard) favored a cortical origin for the mechanism of attention and considered that the brain stem centers had a general awakening function. Jasper agreed with Adrian, emphasizing that the convergence of collateral fibers from the various senory tracts upon the reticular formation is an important consideration.

Hess (Switzerland) brought forward the arguments for looking upon sleep as an active process, not merely the lack of wakefulness and attention. Gastaut (France) gave evidence from lesions in human brains that there are subcortical regulators of cortical activity. He has found lesions in the midbrain which seem to cause bilaterally synchronous discharges to the cortex, accompanied by impairment of "consciousness." Walter (England) described experiments on human subjects who showed variations in cerebral activity as seen by the toposcope. He found distinct changes in the brain potentials in states of boredom and fatigue as opposed to novelty, suspense, interest, and alertness.

Penfield (Montreal) discussed these various points of view in relation to his hypothesis of "centrencephalic integration." He believes that "an area of final functional integration must exist in a ganglionic area in which that stream of nervous impulses must arise that produces voluntary activity." This he considers the "highest level of integration" and locates it in the diencephalon or upper brain stem. Here are to be found those mechanisms which "are prerequisite to the existence of intellectual activity and prerequisite to the initiation of the patterned stream of efferent impulses that produce the planned action of the conscious man." "It is obvious that the most important part of this integration does not take place in the cerebral cortex." "Any portion of the cerebral cortex can be removed without producing unconsciousness. On the other hand, injury to the brain stem does result in unconsciousness."

Fessard (Paris) reviewed philosophically the arguments against the concept of a center of consciousness, but he felt that there must be a neuronal basis and hence some location. He believes that it makes our understanding clearer if we attach consciousness to a center than if we look on it as the result of a distributed activity. And he quotes Herbert Spencer: "The seat of consciousness is that nervous center to which mediately or immediately the most heterogeneous impressions are brought." Penfield also uses this quotation. Fessard considers the mass of neurones with short axones in the reticular formation of the brain stem to be the best mechanism for bringing together present and past experience to form a whole. He considers it an ideal integrating mechanism, where impulses can be brought together spatially and coordinated temporally.

CENTRENCEPHALIC SYSTEM

It seems to me that much of the disagreement is due to lack of clear definition. I believe that both Penfield and Fessard confuse the concepts of "mind" and "consciousness."

As I clearly state in the paper [9] which Fessard criticizes, they are not the same thing. "Consciousness" is one attribute of mind; that part that has to do with awareness of self and of environment It varies in degree from moment to moment in man, and from amoeba to man in phylogeny. As Schiller [10] says, "Consciousness can have no seat, any more than terms like circulation or contractility." It is a function that we cannot quantify, because it is purely subjective, but we can deduce much about it from an organism's behavior. It is a function distinctly on the sensory or input side of the integrating mechanism.

When Penfield and Fessard are talking about the place where past and present experience join and are made available to institute action, they are talking about "mind," not "consciousness." Of course there is some localization of such functions. They are integrated more in some parts of the central nervous system than others—certainly more in brain stem and cerebral cortex than in cerebellum and cord. But still, mind is a function of the living brain in action. It is the integration itself, the relationship of one functioning part of the brain to another. As such it cannot be relegated to a center, or even to a level. If we seriously believe in the recent advances in neurophysiology which indicate that the brain is equipped with extensive feed-back mechanisms and reverberating circuits of neurones, we should expand our concept of a "center." Even "levels" become too restricting, because sequences of impulses in time have to be taken as major considerations. These circuits are now proved by anatomical and physiological observations. They range all the way from the recurrent collaterals of axones to the complex thalamocorticostriatal circuits. When dealing with such mechanisms and such concepts, one must modify his thinking about "higher and lower" or "higher" levels. A circle has no top. Is New Zealand really "down under," or is it on top of New England? Certainly there are differences in complexity and in the number of neurone circuits that impinge on certain cerebral areas. In this sense the reticular formation of the brain stem stands out as one of the most complex. But I do not believe that any one "area for final functional integration" exists. Integration, by its very nature, cannot be "final," and one part of an integrated whole is not more "important" than another, unless one specifies important for what. To my mind (sic) the discriminative function of the cortex is just as essential as the coordinating function of the ventral thalamus—neither could function without the other.

I agree that the "planned action of the conscious man" is the essence of civilized behavior, but I do not consider that one should think in terms of "conscious" or "unconscious," ‡ "planned" or "involuntary." These parts of mental activity are not to be taken as either present or absent. They are matters of degree. Penfield says that "Any portion of the cerebral cortex can be removed without producing unconsciousness." I would say that no considerable portion of the cerebral cortex can be removed without reducing consciousness.§ Small lesions in certain parts of the brain stem only produce somnolence or other partial losses of consciousness.[12] Here, too, it is a matter of degree. Consciousness is an attribute of mind that seems to become more prominent as the brain becomes more and more complex in the ascent of the phylogenetic scale. It can only be proved to be present in man and that only by personal experience and introspection. It can, however, be inferred to be present by behavioral evidence in other men and other animals.

Planned or voluntary action as opposed to involuntary action is also not a matter of either-or, but of degree. I believe that volition is made possible by choice. The organism, by means of the brain, makes innumerable choices every hour. These choices are more or less satisfying to the organism; if satisfying, a feed-back mechanism confirms them, and the confirming reaction is a kind of reward. Thus one educates himself and is to some extent responsible for the result because

‡ "Consciousness" is here used to mean "awareness of self and of environment."

§ References 3 and 11.

of past choices.[13] Even the lowly amoeba has to make choices, but it is only the higher animals, in which encephalization has taken place, that develop mechanisms for conditioning reflexes, storing memories, and making abstractions. Then only does volition become an important problem, with all its philosophical implications.

EMOTIONS, STRESS, AND PHYSIOLOGICAL REACTIONS

What is the idiosyncratic component ‖ in the development of human personality? One of the most discussed problems in psychosomatic medicine is this: Why does a psychogenic symptom strike one organ or system of organs rather than another?¶ Why does one person under emotional stress have headache, another vomit, and a third produce eczema? The oldest and simplest explanation is that of Adler. His theory of "organ inferiority" impressed physicians for some years in the 1920's. In all probability it is a good explanation for some cases; there are certainly inherited tendencies to disorder of special organ systems that seem to be brought out and developed into overt symptoms by environmental stress. Certain cases of migraine and stammering are two good examples; thyrotoxicosis is a disease that runs in families and is precipitated by emotional stress. In such cases this "organ inferiority" concept seems to hold, but it is far from the whole story. There are many anatomical deviations from the average that do not bother some people but that become the center of neurotic reactions in others. Take, for example, such hereditary characteristics as shortness, tallness, myopia, or baldness. Most persons accept the deal that inheritance gives them and do the best they can to enjoy life without too much ado about it. Others use these genetic gifts as scapegoats; they allow neurotic adjustments to focus on them and adversely affect their behavior. Every physician knows the patient who talks of "my headaches" and uses them to escape irksome duties. Everybody knows the sort of little man who is pompous, pretentious, and a little too smart to be bearable. The world is full of people compensating well or badly for inherited traits. Most of them are not medical problems. But those that come to the physician or psychiatrist for help should not be classified as "constitutional inferiors" and therefore hopeless. Some doctors still think that all "neurotics" are "inferior." The fact is that practically everyone has some inferior organs and some neurotic maladjustments. The fact that a disorder, lesion, or anomaly is inherited is no cause for therapeutic pessimism. There are effective treatments for migraine, both medical and psychiatric. Psychotherapy can help people to live with their weaknesses without exploiting them neurotically. Of course there are many cases in which the hereditary load is too heavy; feeblemindedness and blindness, for example, are hereditary handicaps too severe to allow for normal adjustment.

The main interest of psychosomatic research, however, is directed at the emotional components in a number of severe medical illnesses, such as hypertension, asthma, peptic ulcer, and ulcerative colitis. In all of these there is probably a complex combination of causes, with several steps in each physiological sequence. Direct psychological connections between emotions and lesions are not to be expected.

Wolff,[15] in a remarkably thoughtful and concisely written monograph of 200 pages, summarizes a mass of important work done by his group at Cornell. He defines stress and describes the patterns of human reactions set in motion by it; the reaction utilized depends upon the person's nature and past experience. When appropriately used they lead to normal adjustments, but they may be conditioned by untoward circumstances and lead to inappropriate reactions, both qualitatively and quantitatively. This causes "disease."

One of these reactions (called adaptive and protective by Wolff) is that of preparation for receiving food by an infant, i.e., the hunger reaction of gastric hypermotility, hyperemia, and hypersecretion. Another is the

‖ Weider,[14] p. 128.

¶ Weider,[14] Ch. 13 and 14.

protective pattern of defense in the upper respiratory tract, in which air passages are shut by congestion and washed by excessive secretion to keep out such noxious agents as dust. Also one must mention the well-known preparation for fight or flight, described by Cannon, the sympathetic-adrenal emergency reaction, with its rapid heart rate and respiration, raised blood pressure, and muscular tension. More recently this has been supplemented, for more prolonged stress, by Selye's "alarm reaction" and general adaptation syndrome.# All of these are normal reaction patterns, but they may become harmful if associated in youth with frustration, fear, and anger. Thus the normal hunger reaction of the stomach could be repeatedly frustrated by delayed feedings, so that resentment later in life would, by the mechanism of conditioning, set up hyperemia, hypermotility, and hyperacidity that might lead to gastric ulcer. The shutout-and-washout reaction of the respiratory passages could be conditioned so that grief would be associated with respiratory obstruction and lead to attacks resembling asthma. The preparations for a fight, if it never led to anything except anxiety, might get conditioned so that one of the palpitation-hypertension syndromes came on.

A book published by the Army Medical Graduate School, entitled "Symposium on Stress," [16] brings out some new and important points of view. Cannon believed that such strong emotions as rage and fear could not be distinguished from each other by physiological means; the preparation for fight or flight had similar reactions in the neuroendocrine system. This can no longer be considered true. There is good evidence now from von Euler * and Redgate and Gellhorn [17] that epinephrine and arterenol can be secreted selectively and independently by the adrenal medulla. In fact, von Euler's most recent work † indicates that stimulations of a dorsal area in the hypothalamus causes an excess of epinephrine to be excreted, while stimulations of an area slightly more ventral brings out an excessive amount of arterenol. The great importance of this discovery to psychiatry is seen when the observations of Funkenstein ‡ on human subjects are considered: he showed that students subjected to psychological stress either reacted with overt rage ("anger out") or depression ("anger in") or anxiety. Those in the "anger out" group showed physiological reactions indicating a secretion of arterenol, while those in the "anger in" group and anxiety groups showed the reactions characteristic of epinephrine secretion. There is confirmation of this in studies of different animal groups. The carnivorous hunters, like the lion, show a great excess of arterenol in the adrenal secretion, while timid animals that gain safety by flight, like rabbits and antelopes, secrete much more epinephrine. Social animals, for example, monkeys, are on the epinephrine side. Man is apparently a combination and is not bound to one reaction. The human fetus secretes mostly arterenol and only later produces epinephrine. Perhaps "anger out" with its accompanying arterenol is to be looked on as the more primitive reaction.

Weider,[14] Ch. 11.

* In Symposium on Stress.[16]

† Folkow, B., and von Euler, U. S.: Personal communication to the author, Stockholm, 1954.

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Case Reports

PRIMARY VARICELLA PNEUMONIA

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PRIMARY varicella pneumonia in adults is a rare and severe disease. It is the purpose of this report to present a case, review the literature, and discuss the typical clinical picture.

REPORT OF A CASE

A 25-year-old Negro housewife was admitted to the University of Virginia Hospital on March 22, 1954, in acute respiratory distress. Four days prior to admission she had noted a vesicular eruption, beginning behind the ears and spreading over her face and upper chest. She consulted her local physician on the first day, who told her she had chickenpox and gave her acetylsalicylic acid (Aspirin). The following day she developed fever, dyspnea, and cough productive of profuse amounts of mucoid blood-flecked sputum. The rash spread over her entire chest, arms, and abdomen, and she had increasing dyspnea and prostration. Her physician referred her to the hospital on the fourth day of her illness. She had never had chickenpox previously and had been in excellent health.

Physical examination showed a temperature of 101 F. rectally, pulse rate 120, respirations 60, and blood pressure 120/80. She was a well-developed young Negro woman, acutely ill and in marked respiratory distress. She was cyanotic, tachypneic, and dehydrated. Her skin showed typical varicella vesicles, with some crusting over the face and upper chest and erythematous papules over the arms, palms, and abdomen; there were a few vesicular lesions in the posterior pharynx, and the tongue was dry. Shotty generalized lymphadenopathy was present. The lower two-thirds of the chest was filled with medium sticky rales bilaterally. The heart revealed a sinus tachycardia and a Grade 2 apical systolic murmur. The rest of the physical examination was within normal limits.

Laboratory studies on admission showed hemoglobin to be 18 gm.; hematocrit level, 63%; white blood cell count, 11,700. The differential count showed 2 juvenile forms, 23 band cells, 33 segmented forms, 11 large lymphocytes, 29 small lymphocytes, 1 monocyte, and 1 basophile. Urinalysis showed a specific gravity of 1.020, pH of 5, 2+ protein, and an occasional white blood cell. Blood urea was 32 mg. per 100 cc., chlorides 93 mEq. per liter, and CO_2 18.9 mEq. per liter. Chest x-ray showed a diffuse nodular infiltration bilaterally (Fig. 1). On the second hospital day the hematocrit level was 41% and hemoglobin was 12.5 gm.; total proteins were 5.9 gm.; A/G ratio, 1.1:1. Sputum and throat cultures revealed normal flora with alpha hemolytic Streptococcus and Neisseria species present. Several blood cultures showed no growth. Three 24-hour sputa examinations were negative for acid-fast bacilli on concentrated smear. Acute and convalescent sera for psittacosis, Q-fever, and atypical pneumonia were negative, as were cold agglutinins. An electrocardiogram was done on the third hospital day and was normal.

The patient was in critical condition and was immediately placed in an oxygen tent with high humidity. She was hydrated with 5% dextrose in water and was given tetracycline, 0.5 gm. every six hours, to decrease secondary infection. She was seen by a dermatology consultant, who concurred in the diagnosis of chickenpox. Her respirations were less labored while in the oxygen tent, and two hours after being placed in the tent her CO_2 was 25.2 mEq. per liter. She continued to bring up profuse amounts of mucoid sputum, mixed with crusts and bright red blood. Arterial oxygen saturation was determined on the fourth hospital day, while she was out of the tent. This was 85.5%. She slowly improved and by the seventh hospital day was afebrile, breathed much more easily, had fewer rales in the chest, and was removed from the oxygen tent. On the eighth day the tetracycline was discontinued. Serial chest films showed some clearing of the infiltration in the peripheral portions of the lungs by the 10th day. The skin lesions improved as her respiratory reserve increased, and she was discharged on the 12th hospital day. Follow-up x-rays revealed complete clearing by April 30, 1954, five weeks after admission to the hospital, except for a few faint reticular streaks in the left base (Fig. 2).

COMMENT

Chickenpox is traditionally considered to be a mild disease. However, the varicella virus may involve many organs, including

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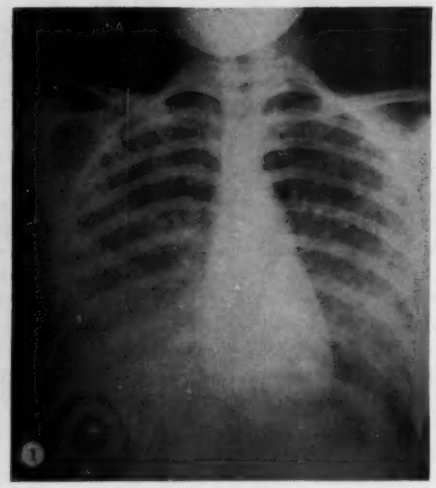


Fig. 1.—Roentgenogram taken on admission, showing extensive diffuse nodular infiltration bilaterally.

the lungs, and may cause a severe and often fatal illness, especially in adults. Primary varicella pneumonia is not mentioned in most textbooks of medicine or pediatrics, and most cases of pneumonia associated with chickenpox have been thought to be the result of secondary bacterial invasion. Bullowa and Wishik,[1] in 1935, described 21 cases of pneumonia associated with 2,534 cases of chickenpox. These pneumonias were thought to be caused by bacterial invaders, usually a Streptococcus. The bacterial etiology was also suggested by the pathological findings of polymorphonuclear cells and bacteria in the lungs of the eight patients who died in the series.

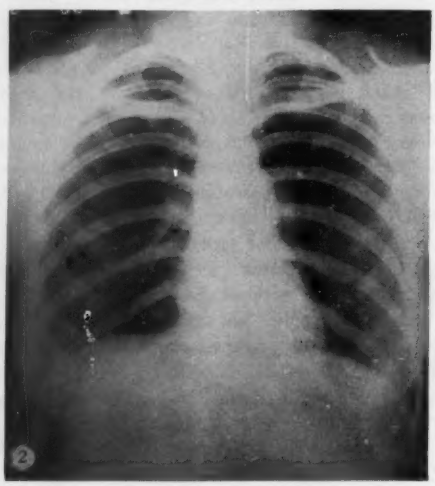
A review of the American literature reveals 15 cases of varicella pneumonia in adults, including this report. Waring, Neubuerger, and Geever [2] first reported two cases in 1942, one of whom died. The 15 cases * illustrate a well-defined clinical entity. The patients were all young adults, aged 25 to 46, except for a 71-year-old woman who was one of the four who died. All were characterized by typical varicella eruption followed in two to six days by increasing respiratory distress, manifested by cough, severe dyspnea, usually some cyanosis, frequently hemoptysis, and varying degrees of prostration. Pneumonitis was demonstrated by physical examination in 13 of the 15 cases; one patient had a normal chest examination, and in one case it was not described. All chest x-rays obtained showed a diffuse nodular infiltration, but no films were described in two cases. The x-ray findings in all surviving cases slowly resolved in from four to six weeks. In no case was the leucocyte count higher than 14,000. Bacteriologic examination of the blood and sputum in the majority of these cases was carried out and yielded no pathogens. Serologic studies in four cases appeared to eliminate atypical pneumonia, psittacosis, and Q-fever as a cause for the respiratory difficulty. All received some type of chemotherapy, with no definite evidence that it influenced the primary disease process. Complications were frequent and severe, occurring in 9 of the 15 patients. There were three episodes of shock, three of congestive heart failure, four of azotemia, one of nephritis, one of encephalitis, and four patients died.

Postmortem examinations were done in the four fatal cases.† These revealed changes which are consistent with a virus pneumonia, with a cellular exudate of large mononuclear

* References 2-12.

† References 2, 6, 8, and 9.

Fig. 2.—Roentgenogram taken five weeks after admission to hospital, showing almost complete clearing of the pneumonic process.



cells, proliferation of alveolar septal cells, hyaline membranes of some alveoli, and areas of necrosis in alveolar cells and arteries. Polymorphonuclear cells and bacteria were scarce. The typical Type A intranuclear inclusion bodies characteristic of chickenpox were found in two cases ‡ in the alveolar septal cells. Eisenbud's case [9] also showed these inclusion bodies in other viscera—the tracheobronchial lymph nodes, liver, spleen, and adrenals. That chickenpox can involve the lungs and other viscera has been well demonstrated by reports of disseminated chickenpox § in which intranuclear inclusion bodies were found in the adrenals, intestines, liver, spleen, kidneys, and thymus, as well as in the lungs.

It seems most likely that these are all cases of primary involvement of the lungs by the varicella virus. The striking similarity in the clinical picture, the paucity of bacterial and serological evidence of other organisms, and the pathological findings in the four necropsied patients all lead to this conclusion. These pathological changes demonstrate the basis of the most striking clinical manifestations of the disease—the severe dyspnea, tachypnea, cyanosis, and hemoptysis which result from the profuse cellular exudate filling the alveoli and small bronchi, with necrosis and ulceration which may even involve the trachea. The poor arterial oxygenation which results was illustrated by an arterial oxygen saturation of 85.5% on the sixth day of pulmonary involvement in the patient in this report.

A variety of antibiotics has been employed to treat these patients. The first cases reported received a sulfonamide and others received all combinations of current antibiotics. In no case did a drug cause a dramatic response, although two cases were reported in which the authors felt the course was shortened by chlortetracycline (Aureomycin).‖

‡ References 8 and 9.

§ References 13-15.

‖ References 7 and 12.

SUMMARY

A case of primary varicella pneumonia in a 25-year-old Negro housewife is reported.

Previously published cases are discussed, and the clinical entity is described. This consists of typical chickenpox followed in a few days by severe pulmonary manifestations, with dyspnea, tachypnea, cyanosis, hemoptysis, and prostration. The chest x-ray reveals a diffuse nodular infiltration. The course is that of slow resolution of the pneumonia, but it is often attended by complications such as shock, congestive heart failure, and azotemia, occasionally by death.

Antibiotic therapy may be of value in decreasing secondary infection, but it has no proved specific effect on the varicella virus.

Dr. Kenneth R. Crispell aided in the preparation of this paper.

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AMYLOIDOSIS UNASSOCIATED WITH A PREDISPOSING DISEASE

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VIRCHOW,[1] in 1854, was the first to describe amyloid. The similarity of the staining properties of amyloid and starch with iodine and sulfuric acid prompted him to name the substance "amyloid." Several years later, Wilks [2] described, in a paper entitled "Cases of Lardaceous Disease and Some Allied Infections," 2 cases, of the 36 presented, in which the autopsy findings were compatible with what was later classified as "primary" systemic amyloidosis. Wild,[3] in 1886, reported the next case of amyloidosis.

"Primary" systemic amyloidosis is a relatively rare condition. In 1929 Lubarsch [6] reported three cases of "primary" systemic amyloidosis and suggested criteria for the recognition of the disease. He also formulated a classification of the various forms of amyloidosis which is still in wide use today. By 1930 only 10 cases had been recorded in the literature. Koletsky and Stecher,[7] in 1939, reviewed the 23 reported cases and added an additional case. Six years later, Lindsay and Knorp [8] summarized 16 additional cases and presented another example, and Lindsay [9] reviewed a total of 45 cases the following year. Later that year Eisen [10] commented on 46 hitherto reported cases and added 2 additional ones. Dahlin [11] collected 57 cases in 1949 and personally added 6 more cases. In 1950 Higgins and Higgins [12] summarized 71 previous cases and added another. Since then, at least 23 more case reports of "primary" systemic amyloidosis have appeared in the literature.*

A review of the literature and a detailed analysis of the published cases of "primary" systemic amyloidosis reveals that the tinctorial characteristics and organ distribution of the amyloid deposits are very frequently indistinguishable from those in the so-called "secondary" form of this disease. This not only instills confusion in regard to classifications based on these criteria but raises the question of whether the tinctorial and localization characteristics of the deposit should be deemphasized as a means of differentiation and, instead, a unitary concept be established. The following case report emphasizes these principles and also serves as a means for discussion and possible reevaluation of the confusing classifications which have clouded the pathological and clinical concepts of the disease.

REPORT OF A CASE

A 51-year-old white salesman was admitted to The Mount Sinai Hospital on April 15, 1951, because of "low back" pain and weakness of both lower extremities since August, 1950.

The family history and past history were negative for hepatic disease, tuberculosis, diabetes, and hypertension. The patient rarely indulged in alcoholic beverages.

The patient was well until August, 1950, when he developed pain in his lower back, with radiation to the left buttock. He also noted weakness of both lower extremities. There were no other focal or generalized symptoms.

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* References 13-31.

On physical examination the patient appeared well developed and well nourished and complained of pain in the lower portion of his back. The temperature, pulse, and respiratory rate were normal. The blood pressure was 134/78. No skin or mucous membrane lesions were noted. The tongue was not enlarged. No abnormalities of the heart or lungs were detected. The abdomen was not distended, and the liver and spleen were not palpable. There was no peripheral edema. Neurological examination revealed bilateral lower extremity hyperreflexia, with a sensory level at T-10. Lower thoracic spine tenderness was present, but no other areas of bone tenderness could be demonstrated.

The hematological, urinary, and blood chemistry data obtained during the present and later hospital admissions and during the patient's ambulatory periods are summarized in Tables 1, 2, and 3.

A lumbar puncture showed a complete block and an ethyl iodophenylundecylate (Pantopaque) myelogram demonstrated an arrest at T-10 (Fig. 1). Total protein in the spinal fluid was 145 mg. per 100 cc.

On April 10, 1951, a laminectomy was done by Dr. S. Gross and an epidural tumor invading the surrounding fat and bone was found extending from T-7 to T-10. The tumor was completely removed. The pathological report, by Dr. S. Otani, was "'Amyloid tumor.' Diffusely infiltrated by amyloid with large number of giant cell reaction. No evidence of neoplasm found." The postoperative course was uneventful, and the patient was discharged on April 21, 1951, completely asymptomatic. He resumed working four weeks later.

He was well until June, 1952, when his appetite became reduced and he developed postprandial nausea. He reduced his food intake and lost 15 lb. (6.75 kg.). Generalized weakness appeared, and he was again admitted, on Sept. 9, 1952, to The Mount Sinai Hospital.

Physical examination was unaltered save for a moderately distended abdomen and a firm smooth nontender liver edge 4.0 cm. beneath the right costal margin. It extended transversely across the abdomen into the medial portion of the left upper quadrant. The spleen and kidneys were not palpable, and no free fluid was demonstrated in the abdominal cavity. X-ray examination of the skull and ribs showed no evidence of a destructive lesion. Both a liver biopsy and Congo red test were refused by the patient, and he was discharged on Sept. 11, 1952, with the diagnosis of amyloid disease with involvement of the liver.

His symptoms of anorexia, nausea, vomiting, easy fatigability, and weight loss persisted. In November, 1952, he developed ankle edema, which subsequently progressed to generalized anasarca with ascites and epigastric bloating.

Additional findings during his stay at another hospital and during his third Mount Sinai Hospital admission included a blood pressure of 140/100 and a marked increase in the hepatomegaly in April, 1953. Proctoscopic examination; electrocardiogram; roentgen examinations of the chest, skull, and upper thoracic vertebrae; intravenous pyelogram; gastrointestinal series; gall-bladder series; barium enema, and first-strength PPD test were negative. Second-strength PPD test was positive. Abdominal paracentesis yielded 3,000 cc. of whitish-cloudy fluid, with a specific gravity of 1.007 and a total cell count of 90 cells per cubic millimeter, of which 15 were R.B.C., and an albumin content of 0.4 gm. per 100 cc., a globulin content of 0.2 gm. per 100 cc., and a total fat content of 27 mg. per 100 cc. The pathology report of the cell block was "mainly mesothelial cells. No tumor cells found."

Treatment with a high-protein low-calorie low-salt diet, intravenously administered salt-poor albumin, diuretics, parenteral crude and refined liver extract, and a liver concentrate prepared for intravenous use (Intraheptol) did not alter his course of progressive weakness, nausea, vomiting and persistent reaccumulations of ascitic fluid necessitating repeated paracentesis. The impression was of (1) amyloid disease with involvement of liver, kidneys (leading to nephrotic syndrome), alimentary tract, blood vessels, and perhaps heart and lungs and (2) polycythemia (secondary?).

On Aug. 11, 1953, he was admitted for the fourth time to The Mount Sinai Hospital. He was cachetic, emaciated, and nonicteric, with a blood pressure of 180/101. Despite the intraperitoneal administration of radioactive Au^{198} (112.5 mc.), his ascites continued. He became anemic, hypotensive, stuporous, and, finally, comatose. Notwithstanding treatment with 2-acetylamino-1, 3, 4-thiadiazole-5-sulfonamide (Diamox), corticotropin (ACTH), and blood transfusions he died, on Nov. 16, 1953.

The autopsy was performed four hours after death. There was moderate icterus of the skin, sclerae, and mucous membranes. The eyes and ears appeared normal, and the tongue

was not enlarged. There was generalized anasarca, with 4+ edema of the lower extremities and 3+ edema of the remainder of the body. The peripheral lymph nodes were not enlarged and there were no skin lesions.

TABLE 1.—*Results of Blood Studies*

	Peripheral Blood							
Date	Hemoglobin, Gm./100 Cc.	RBC/Cu. Mm.	Hematocrit Level, %	WBC/Cu. Mm.	Platelets/Cu. Mm.	Reticulocytes, %	Sedimentation Rate, Westergren	Bone Marrow
4/ 6/51	10.0	3.82	..	8,700	.....	...	15	.....
9/24/51	....	....	..	.....	.....	...	..	Normal
9/10/52	15.0	....	..	8,250	.....	...	93	.....
12/ 1/52	19.2	6.68	59	6,800	.....	...	7	.....
4/24/53	21.5	5.81	57	13,750	.....	...	..	.....
5/ 6/53	....	....	..	.....	.....	...	..	Normal
6/ 8/53	13.4	....	..	.....	.....	...	..	.....
8/12/53	11.0	3.56	..	11,100	.....	...	..	.....
9/18/53	10.9	4.09	40	5,800	82,000	0.7	..	.....
10/31/53	13.0	3.80	..	4,750	.....	...	..	.....
11/ 2/53	13.0	4.19	..	5,850	.....	...	..	.....

TABLE 2.—*Results of Urine and Stool Examinations**

	Urine									
Date	S. G.	Reaction	Albumin	Sugar	Microscopic Studies	HCl Ring	Bence Jones Protein	P. S. P. Excretion 15 Min.	P. S. P. Excretion 2 Hr.	Benzidine Reaction
4/ 6/51	1.022	Alk.	0	0	1-2 WBC, 0-2 RBC, occasional epithelial cells	....	....	..	..	....
9/10/52	1.021	Alk.	4+	0	0-2 WBC	....	....	..	..	....
12/ 1/52	1.015	.....	3+	..	.....	....	Neg.	40	75	Pos.
5/ 1/53	1.024	Acid	4+	0	3-5 WBC, many hyaline casts	Pos.	Neg.	..	..	....

* Many repeat urine analyses until the patient's death yielded results similar to those in the Table. In addition, many coarse granular casts, an occasional RBC and WBC, and, on one examination, a rare fat cell were seen. On several determinations the urinary albumin ranged between 5.5 and 9.0 gm. per liter.

TABLE 3.—*Results of Blood Chemistry Studies*

Date	BUN, Mg./100 Cc.	Creatinine, Mg./100 Cc.	Uric Acid, Mg./100 Cc.	Cholesterol, Total Mg./100 Cc.	Bilirubin, Mg./100 Cc. Indirect	Bilirubin, Mg./100 Cc. Direct	Alkaline Phosphatase, Units	Total Protein, Gm./100 Cc.	Albumin, Gm./100 Cc.	Globulin, Gm./100 Cc.	Cephalin Flocculation	Thymol Turbidity, Units	Sulfobromophalein Retention After 45 Min.	Prothrombin Time
9/10/52	8	...	...	580	...	...	56	7.1	3.5	3.6	.....	...	.....	.....
				Cholesterol esters, 370 mg./100 cc.										
12/ 1/52	8	...	2.4	...	1.6	<0.1	97	4.4	2.2	2.2	Neg.	1.0	3.1% after 30 min.	21 sec., normal (upper limit)
5/ 2/53	15	...	7.2	450	...	...	116	3.9	1.5	2.4	.....	...	.....	.....
	Total serum mucoprotein, 73.4 mg./100 cc.						Total serum protein-bound polysaccharide, 155 mg./100 cc.							
8/19/53	..	...	...	...	...	...	140	5.8	3.1	2.7	.....	...	.....	.....
9/16/53	45	3.0	...	...	...	...	...	4.8	2.3	2.5	4+	2.7	.....	.....
11/ 4/53	51	2.2	...	...	...	...	...	...	...	...	.....	...	.....	.....
	S. T. S. neg. on two separate determinations													

Two thousand five hundred cubic centimeters of clear amber fluid was present in the peritoneal cavity. Several fibrous adhesions were present between adjacent loops of jejunum and between the lower margin of the spleen and the adjacent jejunum. The lower edge of the liver extended 7 cm. beneath the right costal margin and extended transversely across the

abdomen from the right midaxillary line to the left midaxillary line. The spleen was situated beneath the left lobe of the liver, and the upper poles of both the liver and spleen were attached to their adjacent diaphragmatic leaves by fibrous adhesions. The pericardial and pleural cavities contained the normal quantity of clear amber fluid.

The heart weighed 250 gm. The right ventricle was slightly hypertrophied, and the left ventricle was moderately hypertrophied. There was a dull grayish mottling throughout the

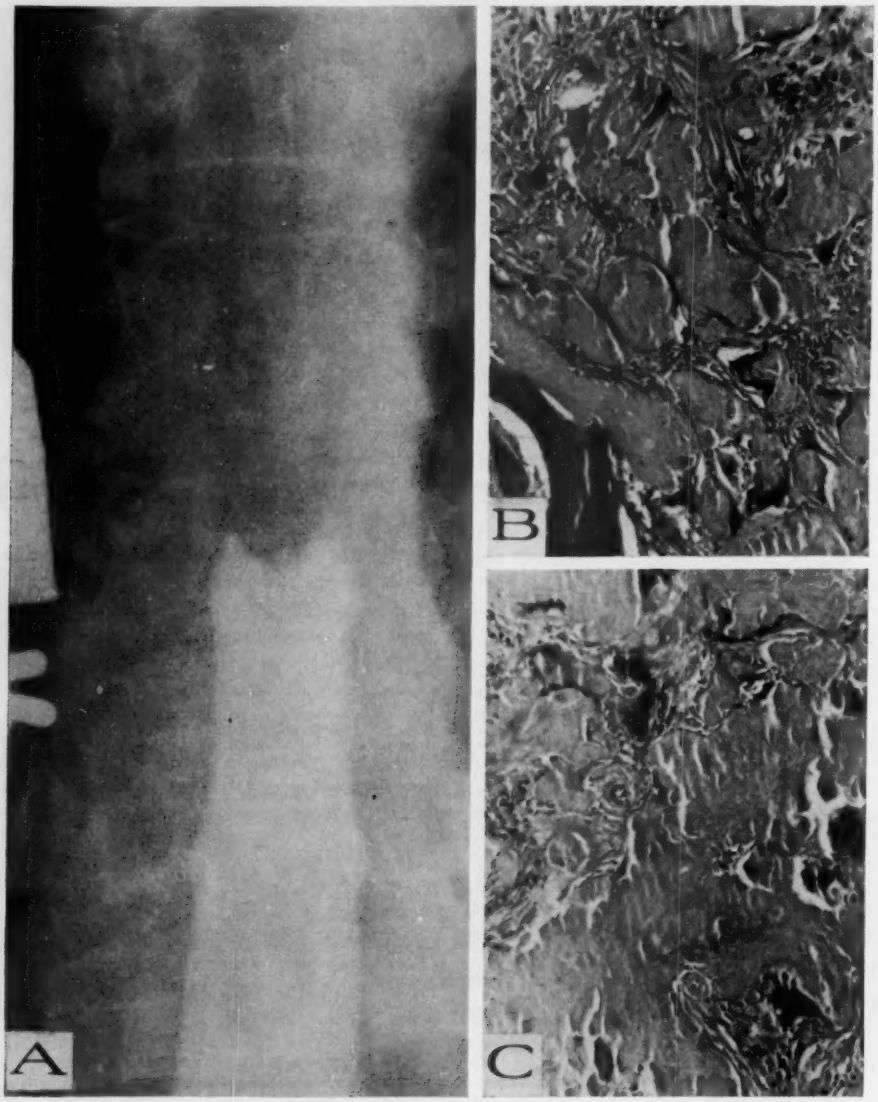

Fig. 1.—*A*, ethyl iodophenylundecylate (Pantopaque) myelogram, showing complete block at T-10. *B*, a tumor-like mass of a portion of bone (vertebra) removed by operation, showing dense deposits of amyloid and destruction of bone trabeculae. Remnant of trabeculae seen at one corner; × 115. *C*, dense amyloid deposits are surrounded by foreign body giant cells; × 115.

normal red-brown of the myocardium. Several small nodules were present on the mitral valve at the line of apposition. The pericardium, atria, and chordae tendinae appeared essentially normal. There was very slight atherosclerosis but no narrowing of the major branches of the coronary arteries.

The lungs together weighed 900 gm. All the lobes of the lungs were moderately emphysematous. The secondary bronchi of the right middle and lower lobes had an erythematous granular mucosa, with a small amount of overlying mucopurulent material. There were no bronchial dilatations or lung abscesses.

Several smooth yellow intimal plaques were present on the descending portion of the aorta and on the pulmonary artery. The portal and splenic veins were slightly dilated, and the mesenteric blood vessels were thicker and firmer than usual. The spleen weighed 320 gm. The capsule appeared slightly thickened. On section the consistency was stony-hard, and a dull translucent grayish white material diffusely infiltrated the parenchyma, obliterating the normal architecture.

The liver weighed 3,650 gm., and the right hepatic lobe was both larger and harder than the left lobe. The capsule was smooth and shiny. The lobular architecture was absent and was replaced by a mottling of red-brown areas upon a dull gray translucent background. The blood vessel walls of the hepatic artery appeared thickened.

The gastrointestinal tract was essentially normal except for many petechial hemorrhages in the gastric mucosa near the cardia.

The right kidney weighed 150 gm., and the left kidney weighed 140 gm. The capsules were normal, and the surfaces were smooth with a reddish-blue color. The glomerular dots were easily seen, and the intrarenal blood vessel walls were prominent. The testes were soft.

The adrenals together weighed 20 gm. Both were extremely firm, with yellow cortices and tan medullas.

There was no change in the size or consistency of the lymph nodes.

Several hard round dull gray translucent areas measuring 5 mm. in diameter were present in the marrow of the lumbar vertebrae.

Histologic examination revealed amyloid deposits in all tissues of the heart. There were slight diffuse and nodular amyloid deposits in the pericardium. Diffuse deposits were also seen in focal areas of myocardial fibrosis and between the myocardial fibers; however, there was no myocardial atrophy. Diffuse amyloid deposits were conspicuously present in the subendothelial portion of the endocardium of both ventricles, and several small amyloid nodules were present on the mitral valve. Almost all the cardial blood vessels contained a moderate amount of amyloid deposited throughout the walls.

Focal areas of bronchopneumonia together with an acute bronchitis were present in the right lower lobe of the lung. A very small amount of amyloid was present in the alveolar septa. Practically all of the pulmonary blood vessel walls contained a slight diffuse deposition of amyloid.

The normal splenic architecture was completely destroyed by diffuse massive deposits of amyloid, with extreme degeneration and atrophy of the parenchyma. Few parenchymal cells remained, and there were diffuse extensive amyloid deposits in the blood vessel walls.

The liver presented a striking histologic appearance. The hepatic architecture was completely obliterated by an extensive diffuse deposition of amyloid between the sinus endothelium and hepatic cells. The liver cells were compressed and distorted by the amyloid deposits and exhibited severe cellular degenerative changes, with atrophy and necrosis. Many of the liver cords were replaced by amyloid, and the blood vessel walls contained extensive amyloid deposits. The amyloid deposits were greater in the right hepatic lobe than in the left hepatic lobe. Extensive diffuse amyloid deposits were seen in the interstitial connective tissue of the pancreas and throughout the walls of the pancreatic blood vessels.

Minimal amyloid deposits were present in the interstitial connective tissue and around the muscle fibers of the tongue. Diffuse deposits were also present in the blood vessel walls. Throughout the esophagus, stomach, gallbladder, and intestines, slight, diffuse, and focal amyloid deposits were seen in the interstitial tissues surrounding the muscle fibers of the muscularis mucosae and muscularis, surrounding the mucosal glands, and in the blood vessel walls. Minimal amyloid deposits were found in both the mesenteric connective tissue and blood vessel walls.

All the glomeruli were almost completely replaced by a diffuse amyloid infiltration, with a variable degree of degeneration and atrophy of the glomerular endothelium. The glomeruli were enlarged, and the capillaries contained little blood. There were also extensive amyloid deposits in the interstitial tissue between the renal tubules, with compression, atrophy, and necrosis of

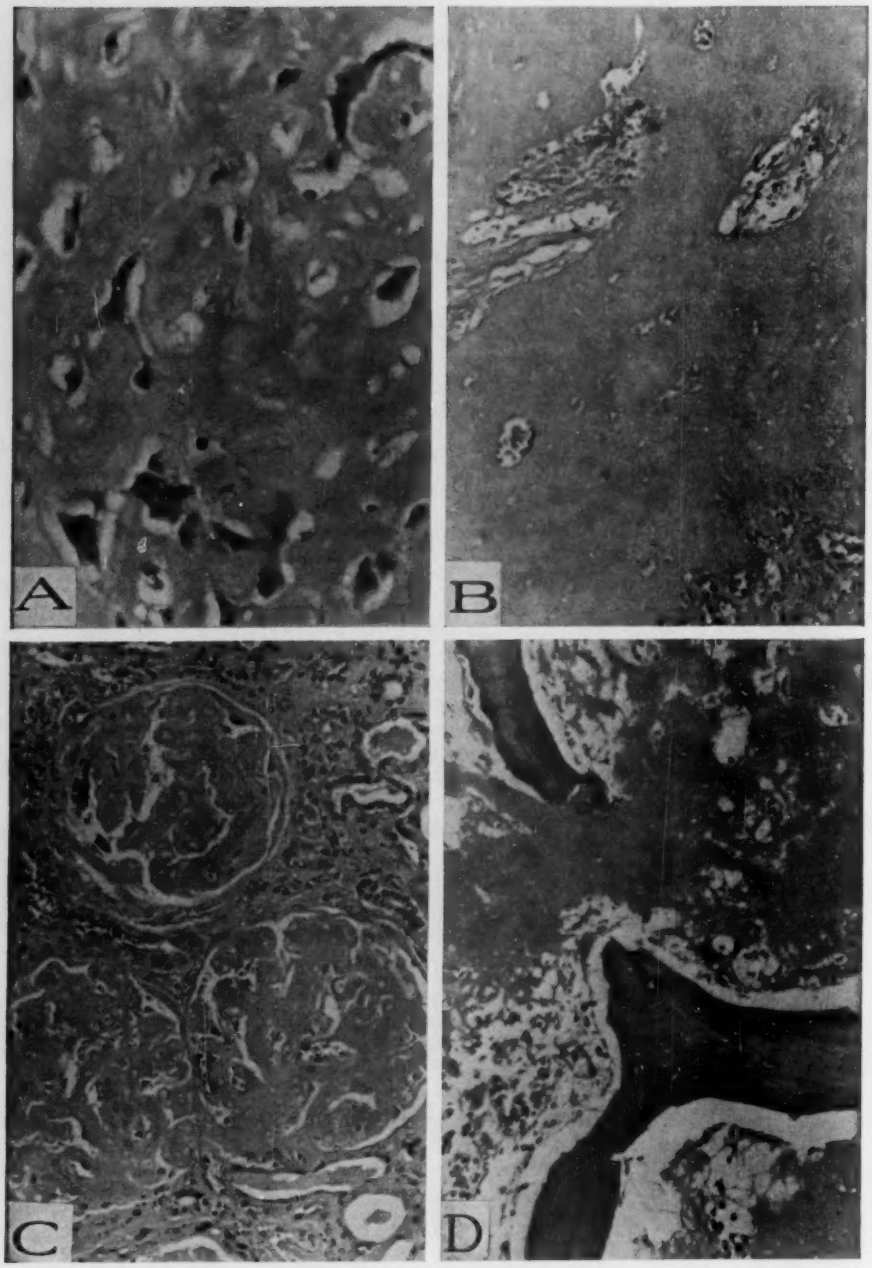

Fig. 2.—*A*, liver. Extremely dense deposits of amyloid. Remnant of deformed liver cells which appear to be atrophic; × 288. *B*, spleen. Extreme degree of amyloid deposits. Remnant of splenic tissue which is hardly recognizable; × 115. *C*, kidney. All glomeruli show marked deposits of amyloid. Glomeruli are closely apposed to each other because of extreme atrophy of renal tubules; × 115. *D*, bone (vertebra, autopsy material). Marrow tissue replaced by amyloid. Trabeculae remain intact; × 115.

many of the tubule cells. Many of the renal tubules were dilated, and the basement membrane was thickened with an infiltration of amyloid. There were no amyloid casts. All the blood vessel walls contained extensive amyloid deposits, but the lumina were not narrowed. There was a slight diffuse amyloid infiltration of the basement membrane and between the spermatic cells of the seminiferous tubules. Focal amyloid deposits were also present in the intertubular connective tissue of the testes.

In the adrenals there were extensive amyloid deposits both in the cortex and in the medulla, with degeneration and atrophy of the parenchymal cells. Extensive amyloid deposits were also present in the blood vessel walls. Both diffuse and focal amyloid deposits were present in the lymph nodes. Slight diffuse amyloid deposits were present around the muscle fibers of the diaphragm and psoas muscles. No amyloid was found in the aorta. The bone marrow of the vertebrae was almost completely replaced by amyloid. Small islands of surviving normal hemopoietic cells were present. After an intensive search no myeloma cells were seen. The bony trabeculae were markedly irregular, and extensive amyloid deposits were present in the walls of the blood vessels and sinusoids.

In almost every section which contained fat tissue, a thin ribbon of amyloid outlining the fat cells was seen. No giant cells or bone formation were seen.

The amyloid stained pink with the hematoxylin and eosin stain and was metachromatic with the methyl violet stain. It stained inconsistently a pale red with the Congo red stain.

Comment.—Both during the patient's life and during many hospital admissions and at autopsy, no disease was found that predisposes to amyloidosis. Although a careful search was made for multiple myeloma, there was no evidence whatsoever for this disease. This is, therefore, a case of amyloidosis unassociated with a predisposing disease. Many provocative problems are present of which the progression of an "amyloid tumor" to diffuse amyloid disease; the extensive amyloid deposits in liver, spleen, and kidneys, with resultant hepatic and renal manifestations; the diffuse bone marrow involvement and associated erythrocytosis, and the artificial classification of amyloid disease into so-called "primary" and "secondary" amyloidosis are points for discussion.

AMYLOID TUMOR AND DIFFUSE AMYLOID DISEASE

Many reports are available of so-called "amyloid tumors," but tumor-forming amyloidosis of the vertebral column is rare. Mandl [45] and Bauer and Kuzma [46] have each described a case of this type. "Amyloid tumors" of bone unassociated with a predisposing disease have been reported by several additional authors.† In several of the cases that came to necropsy amyloid was found at other sites. In many case reports of amyloidosis restricted to the heart, amyloid deposits were also found in other viscera at autopsy.‡

Three cases § are present in the literature of patients whose presenting complaint was referable to a local, tumor-forming amyloidosis of the bones and who at necropsy were found to have amyloid deposits in other tissues.

It appears, therefore, that localized "amyloid tumors" not associated with presumed etiologic disease may be a manifestation of a subclinical generalized, diffuse amyloidosis, and it is not unlikely that many amyloid tumors of this nature will eventually, after a variable interval, be associated with a generalization of the disease.

AMYLOIDOSIS AND ERYTHROCYTOSIS

There was a diffuse, extensive amyloid infiltration of the bone marrow of this patient. Amyloid deposits were also found in the walls of the bone marrow arteries.

† References 4 and 47-50.

‡ References 32, 36, 40, and 50.

§ References 7, 48, and 51.

The patient was anemic at the time of the surgical removal of his amyloid tumor in April, 1951, and in September, 1952, when he first manifested signs and symptoms of generalized amyloidosis, his hemoglobin was 15.0 gm. per 100 cc. His erythrocytosis progressively increased, reaching a hemoglobin value of 21.5 gm. in April, 1953. At this time his plasma volume was 3,700 cc., or 55 cc. per kilogram body weight, slightly elevated, and his total blood volume was 8,600 cc., or 130 cc. per kilogram body weight, markedly elevated. His hemoglobin and hematocrit values and red blood cell count subsequently declined, and blood transfusions were necessary to maintain his hemoglobin level at approximately 13.0 gm. In the absence of any clinical, laboratory, or postmortem findings indicative of polycythemia vera, the erythrocytosis was probably indicative of a secondary polycythemia. At no time was there evidence of congestive heart failure, heart disease, or pulmonary physiological impairment. With the exception of the minimal amyloid deposits in the alveolar septa and alveolar blood vessels, the lungs were not otherwise diseased. Perhaps amyloidosis of the bone marrow blood vessels with resulting bone marrow hypoxia was the stimulus for the erythrocytosis seen in this patient, and it is probable that the terminal anemia, requiring blood transfusions to maintain the hemoglobin level, was on a myelophthisic basis secondary to the extensive diffuse bone marrow amyloidosis.

RENAL AMYLOIDOSIS

Extensive renal involvement in amyloidosis unassociated with a predisposing disease is not unusual. Cases have been reported by Golden,[57] Pocock and Dickens,[30] Goldman and Gersti,[15] Zemp,[44] Mattlaus,[58] Lindsay and Knorp,[8] Terbrüggen,[59] and others. Renal insufficiency with azotemia was present in the cases of Bannick and co-workers,[35] Perla and Gross,[60] Brown and Selzer,[61] Dahlin,‖ Iverson and Morrison,[62] Eisen,[10] Williams,[55] and Parker and co-workers.[12]

The association of a nephrotic syndrome [5] with amyloidosis of the kidneys unassociated with a predisposing disease has been reported, prior to this case report, by three investigators.¶ A possible case is mentioned by Platt and Davson,[4] but the scanty histologic data given does not permit us to place it unequivocally in this group.

In the case presented in this paper, the patient developed renal insufficiency with azotemia and hypertension approximately three years after his first symptoms. The elevation in blood pressure appears to have antedated the azotemia by several months. If one does not accept the case of Platt and Davson [4] because the difference in weight of the kidneys suggests unilateral chronic renal disease, this case represents the fourth case of amyloidosis of the kidneys unassociated with a predisposing disease giving rise to the nephrotic syndrome. Furthermore, it is the second reported case of hypertension and the nephrotic syndrome associated with amyloid kidneys of this type. The kidneys in this case weighed 150 and 140 gm., respectively. The kidneys in Williams' case [55] weighed less than normal. In both cases there were extensive amyloid deposits in the renal blood vessels.

HEPATIC AMYLOIDOSIS

There are many reports in the literature of amyloid deposits in the liver parenchyma in amyloidosis unassociated with a predisposing disease. Extensive involvement of the liver has been reported by Husten,[52] Bannick and co-workers,[35] Orloff

‖ References 11 and 39.

¶ References 8, 55, and 63.

and Felder,[42] Eisen,[10] Zetzel,[54] Zemp,[44] Berris and Wolff,[56] Ballinger,[32] Dahlin,# Wollaeger,[41] Higgins and Higgins,[12] and Graham.[17] Less extensive hepatic amyloid deposits have been reported by other observers.*

There are few published reports concerning liver-function studies. In our case the sulfobromophthalein test and prothrombin time were within normal limits. The serum globulin was 3.6 gm. per 100 cc. initially and on subsequent examinations was normal. There was marked proteinuria, and the serum albumin was reduced. The cephalin-cholesterol-flocculation test was negative, 4+, and 1+ on three determinations. The thymol turbidity was 1.0 and 2.7 units on two determinations. The serum alkaline phosphatase in our patient progressively rose from 56 to 140 K. A. units per 100 cc. Gutman [53] has noted that the serum alkaline phosphatase may be markedly elevated in patients with hepatic amyloidosis. In our patient with extensive amyloidosis of the bones and liver the markedly elevated serum alkaline phosphatase level of 140 K. A. units per 100 cc. is undoubtedly a reflection of the amyloid deposits in these organs.

CLASSIFICATION OF AMYLOID DISEASE

In 1893 Wichmann [33] classified amyloid disease into "local" and "generalized" forms. Lubarsch [6] in 1929 recommended that amyloidosis be classified as "typical" and "atypical." His criteria were formulated on alleged differences in both the tinctorial characteristics and the localization and quantity of the visceral amyloid deposits together with the presence or absence of a preceding or concomitant disease to which the amyloidosis may be ascribed. Reimann, Kousky, and Eklund [34] in 1935 proposed that the disease be divided into the following categories: "I. Primary amyloidosis, II. Secondary amyloidosis, III. Tumor-forming amyloidosis and IV. Amyloidosis occurring with multiple myeloma." Their criteria for differentiation into these divisions were similar to those of Lubarsch. Similar classifications have been proposed by King,[36] Rosenblum and Kirschbaum,[37] and Dahlin.[38] To add to the confusion, the following synonyms have been used for "primary" amyloidosis: "unusual," "idiopathic," "systematized," "para-amyloidosis," "diffuse," "generalized," "atypical," "primary atypical," etc.† Synonyms used by various authors for "secondary" amyloidosis are "typical," "genuine," "visceral," "generalized," "parenchymatous," etc.‡

Our case exhibits features which are not only provocative but which actually throw doubt on the validity of the criteria used by the previous authors in the classification of amyloid disease. We have been impressed with the common misconception in the literature that in "primary" amyloidosis the location of the amyloid deposits is restricted predominantly, if not exclusively, to the areas cited by the above authors. A review of the literature reveals many cases of "primary" amyloidosis with extensive amyloid desposits in areas supposedly involved only in "secondary" amyloidosis. In fact, a tabulation of the tissues and organs involved in the published cases of "primary" and "secondary" amyloidosis would show impressive overlapping of visceral involvement in both forms, as is commonly observed in the "secondary" type, and of mesenchymal involvement, as is presumed to occur predominantly in the "primary" form.

References 11, 38, and 39.

* References 30 and 43.

† References 7-10, 12, 13, 15, 16, 18, 23, 26, 30, 31, and 35.

‡ References 34 and 36.

SUMMARY

A case of amyloidosis unassociated with a predisposing disease with extensive parenchymal deposits in the liver, spleen, kidneys, adrenals, and bone marrow and less severe deposits in almost every tissue of the body is presented. The case is characterized by the association of a localized "amyloid tumor" of bone with a subsequently manifest, generalized, diffuse amyloidosis and the development of erythrocytosis followed by anemia during the course of the disease. It is the second reported case of the nephrotic syndrome and hypertension with amyloidosis of the kidneys not associated with a predisposing disease. The validity of the criteria used by previous authors in the classification of amyloid disease is questioned and discussed.

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Scientific Exhibits

FUNGOUS DISEASES

EMMA S. MOSS
ALBERT L. McQUOWN
AND
ROBERT S. COOKE
NEW ORLEANS

FUNGOUS diseases occur world wide. A knowledge of the mycoses, of their signs and symptoms, and of correct treatment is vital for the modern clinician. He is the person who considers them in the differential diagnosis. The definitive diagnosis can only be accomplished in the pathological laboratory. It is imperative that an accurate diagnosis be made, as the treatment varies with each etiologic agent and specific therapy is now available for many of these diseases. This exhibit presents and summarizes the principal points of the diseases produced by the pathogenic fungi.

Director, Department of Pathology, Charity Hospital of Louisiana at New Orleans, and Clinical Professor of Pathology, Louisiana State University School of Medicine (Dr. Moss); Pathologist, Our Lady of the Lake Hospital, Baton Rouge, La., and Clinical Assistant Professor of Pathology, Louisiana State University School of Medicine (Dr. McQuown); Assistant Pathologist, Charity Hospital of Louisiana at New Orleans (Dr. Cooke).

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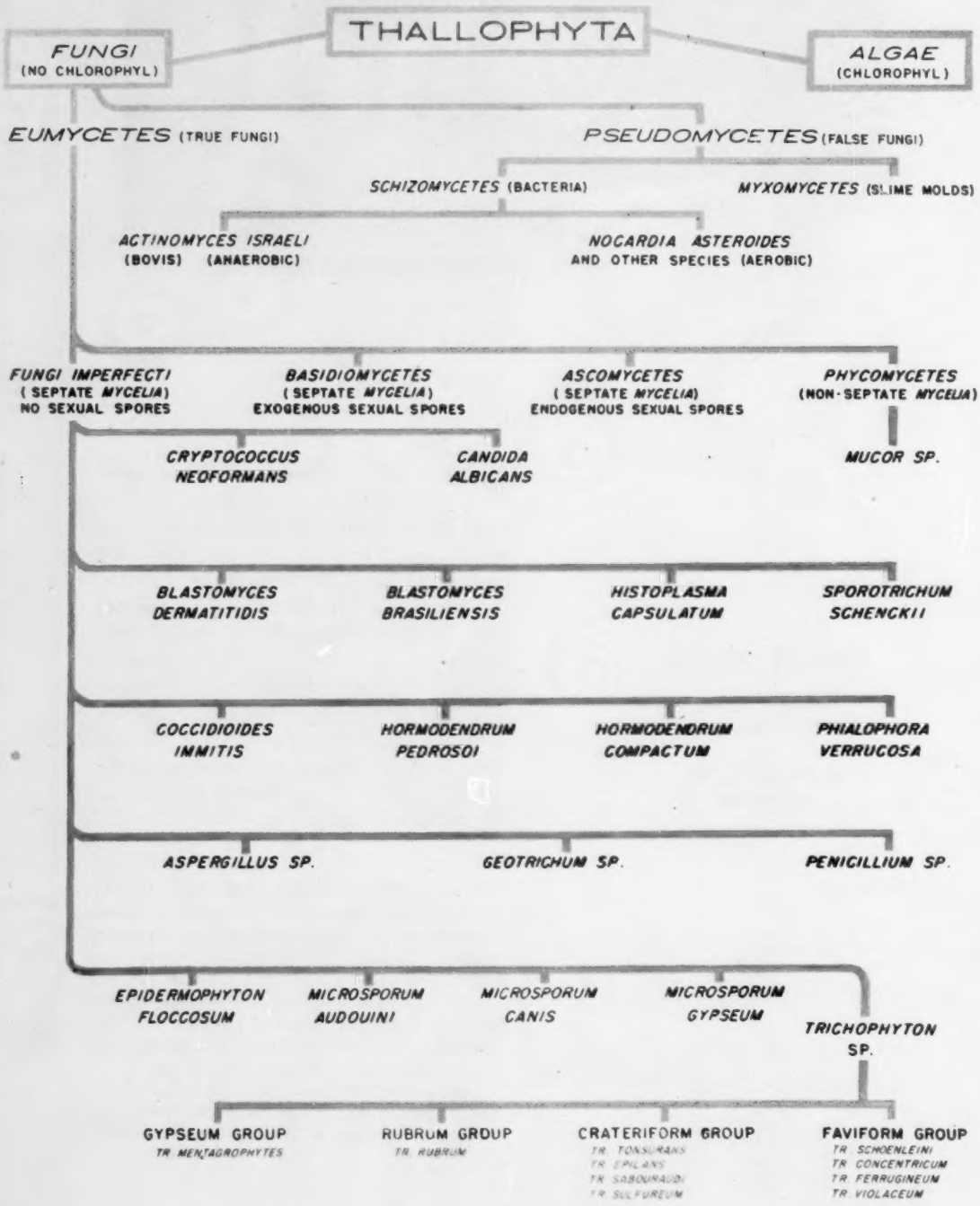
CLASSIFICATION



METHODS OF DIAGNOSIS

CLINICAL SIGNS AND SYMPTOMS (MOST IMPORTANT OF ALL)

AGE INCIDENCE
SEX INCIDENCE
LOCATION OF LESIONS
DURATION OF LESIONS
APPEARANCE OF LESIONS
OCCUPATIONAL HISTORY
GEOGRAPHIC LOCATION (IMPORTANT IN SOME INFECTIONS)

LABORATORY DIAGNOSIS

DIRECT EXAMINATION (PUS, EXUDATES AND SCRAPINGS) STAINED AND UNSTAINED WET MOUNTS, SIMPLEST-MOST IMPORTANT.

CULTURAL METHODS. NECESSARY FOR DEFINITIVE DIAGNOSIS.

HISTOLOGICAL EXAMINATION. GRANULOMATOUS CHANGES, SPORES OR COLONIES OF FUNGI MAY BE PRESENT.

CUTANEOUS TESTS. USEFUL IN COCCIDIOIDOMYCOSIS, BLASTOMYCOSIS, SPOROTRICHOSIS, HISTOPLASMOSIS AND TRICHOPHYTOSIS.

ANIMAL INOCULATION. USEFUL IN SOME SYSTEMIC INFECTIONS.

FERMENTATION TESTS. RESULTS USUALLY POOR.

AGGLUTINATION TESTS. USEFUL IN MONILIASIS AND BLASTOMYCOSIS.

PRECIPITIN AND COMPLEMENT FIXATION TESTS. USED WITH SYSTEMIC MYCOSIS--VALUELESS FOR SUPERFICIAL FUNGI.

FUSION OF MYCELIA (RESEARCH). ONLY STRAINS OF SAME SPECIES WILL FUSE WHEN ALLOWED TO MINGLE.

OTHER AIDS

ROENTGEN EXAMINATION. USEFUL FOR PULMONARY AND BONE LESIONS.

FILTERED ULTRAVIOLET RADIATION. FOR CUTANEOUS FUNGI.

THERAPEUTIC TEST. USED PRIOR TO IDENTIFICATION OF ETIOLOGIC AGENT. SHOULD NOT BE USED.

PROCEDURES FOR MYCOLOGICAL DIAGNOSIS

SPECIMEN

RESULTS MORE SATISFACTORY WHEN SPECIMEN OBTAINED PRIOR TO TREATMENT.
CLEAN SKIN WITH ACETONE FOR SKIN SCRAPINGS.
AVOID CONTAMINATION.

DIRECT MICROSCOPIC EXAMINATION OF SPECIMEN

WET PREPARATION MOST USEFUL.
- UNSTAINED - EXAMINE WITH REDUCED LIGHT.
  - USE MATERIAL AS OBTAINED.
  - SUSPEND IN SALINE IF NECESSARY.
  - CLEAR IN KOH IF NECESSARY.
- STAINED - ADD AQUEOUS STAIN FOR CONTRAST.
- INDIA INK - TO DEMONSTRATE CAPSULES AND DIFFERENTIATE YEAST-LIKE ORGANISMS.

FIXED STAINED PREPARATIONS.
- SCHIFF'S PERIODIC ACID, (HOTCHKISS - McMANUS MODIFICATION).
- HEMATOXYLIN AND EOSIN.
- GRAM'S
- ACID FAST

METHODS FOR CULTURES

MEDIA - ROUTINE:
- LITTMAN'S OXGALL: SKIN SCRAPINGS, HAIRS, SPUTUM, FECES, URINE, CONTAMINATED EXUDATES FROM SINUSES, ULCERS AND ABSCESSES.
- SABOURAUD'S GLUCOSE AGAR: UNCONTAMINATED TRANSUDATES AND EXUDATES; ALSO FOR ANY MATERIAL SUSPECTED OF CONTAINING *ACTINOMYCETES* AND *NOCARDIA SP*.

MEDIA - SPECIAL:
- BLOOD AGAR: *HISTOPLASMA* AND YEAST PHASE OF SYSTEMIC FUNGI.
- BRAIN VEAL INFUSION: AGAR SHAKE TUBES FOR *ACTINOMYCES ISRAELI*.
- CORN MEAL OR CHLAMYDOSPORE AGAR: NECESSARY FOR DIFFERENTIATION OF *CANDIDA ALBICANS*.

TEMPERATURE OF INCUBATION

20° C.
- CULTURES ON LITTMAN'S OXGALL MEDIUM, SABOURAUD'S GLUCOSE AGAR, CORNMEAL AGAR, AND CHLAMYDOSPORE AGAR.

37° C.
- BLOOD AGAR.
- BRAIN VEAL INFUSION AGAR.
  - ANY ORGANISM THAT CAN BE CONVERTED FROM MOLD TO YEAST ON SUBCULTURE.

TIME ROUTINE

OBSERVE 3 TO 21 DAYS.

IDENTIFICATION

CHARACTERISTIC COLONY GROWTH ON MEDIUM OF CHOICE.
WET PREPARATION. CHARACTERISTIC SPORES AND MYCELIUM.
SLIDE CULTURE. CHACTERISTIC GROWTH WITH DEVELOPMENT OF TYPICAL SPORES AND HYPHAE.

CONTAMINANTS

USUALLY GROW MORE RAPIDLY THAN PATHOGENS.

SPREAD RAPIDLY ON SABOURAUD'S MEDIUM.

TEND TO OUTGROW PATHOGENS ON SABOURAUD'S MEDIUM.

ON LITTMAN'S OXGALL MEDIUM TEND TO PRODUCE SMALL, WELL ISOLATED, NON-SPREADING COLONIES.

MAY BE TRUE CONTAMINANTS---- AIR-BORNE.

MAY BE SECONDARILY PRESENT IN LESIONS DUE TO PATHOGENIC FUNGI.

OCCASIONALLY MAY BE ETIOLOGIC AGENT.

MEDIA

LITTMAN OXGALL AGAR: IDEAL FOR PRIMARY ISOLATION ESPECIALLY FOR THE DERMATOPHYTES.

SABOURAUD GLUCOSE AGAR: GOOD MEDIUM FOR ISOLATION FROM UNCONTAMINATED MATERIAL. MAY BE IMPROVED BY ADDITION OF ANTIBIOTICS. EXCELLENT FOR STOCK CULTURES.

CORN MEAL AGAR AND CHLAMYDOSPORE AGAR: USEFUL IN IDENTIFICATION OF *CANDIDA ALBICANS*.

BLOOD AGAR: GOOD FOR CONVERSION TO YEAST-LIKE PHASE AT 37°C. EXCELLENT FOR ISOLATION OF *HISTOPLASMA CAPSULATUM*.

BRAIN HEART INFUSION BROTH WITH AGAR: GOOD FOR ISOLATION AND GROWTH OF *ACTINOMYCES ISRAELI* (ANAEROBIC).

ANY ANTIBIOTIC OR VARIOUS ANTIBIOTICS MAY BE ADDED TO THE ABOVE MEDIA FOR REDUCTION OF CONTAMINANTS. PREPARED DEHYDRATED MEDIA OF THE ABOVE TYPES MAY BE PURCHASED COMMERCIALLY.

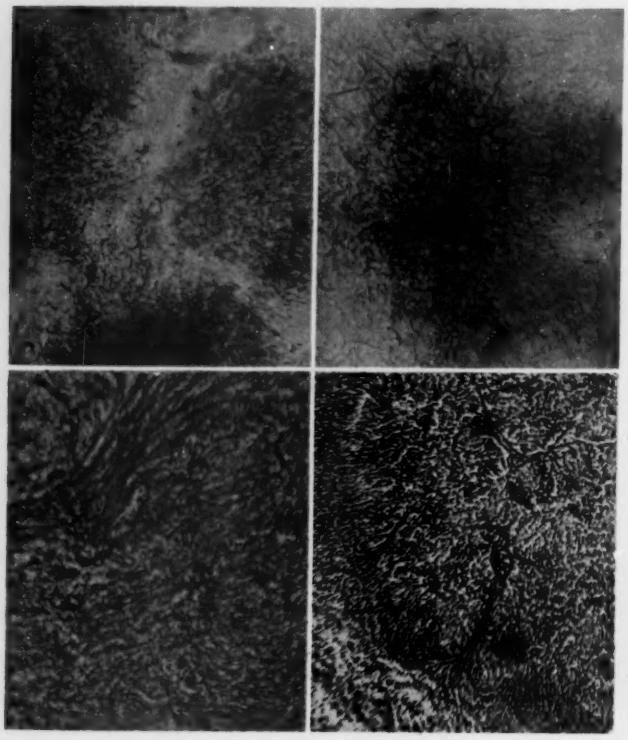
ACTINOMYCOSIS

ETIOLOGIC AGENT:
Actinomyces israeli (anaerobic)

CLINICAL:

Chronic superficial and visceral granulomatous lesions which break down and form multiple sinuses.

MICROSCOPIC EXAMINATION:

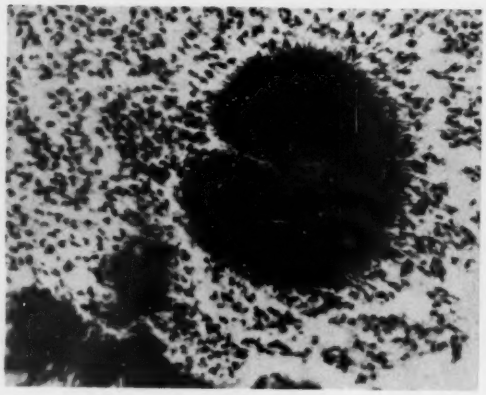


Direct: "Sulfur granules" in exudate; gram-positive branching elements. May or may not have clubbed ends.

CULTURES:

Colony: Grows anaerobicly below the surface of liquid or semi-solid medium; fuzzy, lobulated.
Microscopic: Tangled masses or fragments of delicately branched hyphae. (Bacteria-like.)

HISTOPATHOLOGY:



Granuloma: Characteristic "granules" found in cellular exudate.

TREATMENT:

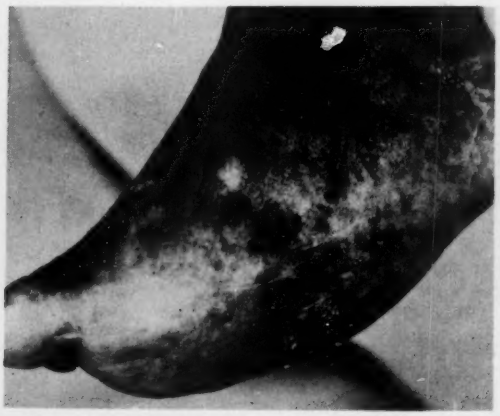
Surgical excision.
Medical: Penicillin; sulfadiazine; chlortetracycline; chloramphenicol; streptomycin.

DISTRIBUTION: World wide.

NOCARDIOSIS

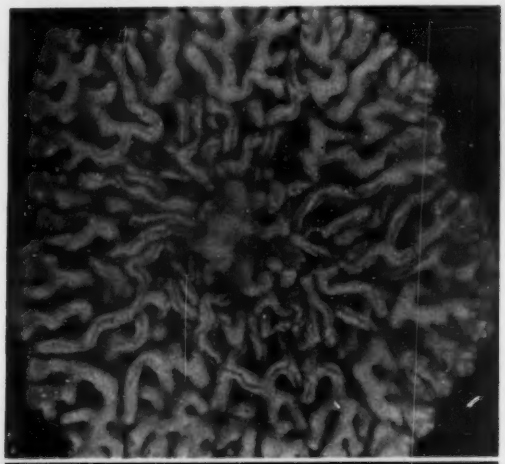
ETIOLOGIC AGENT:
Nocardia asteroides (aerobic).

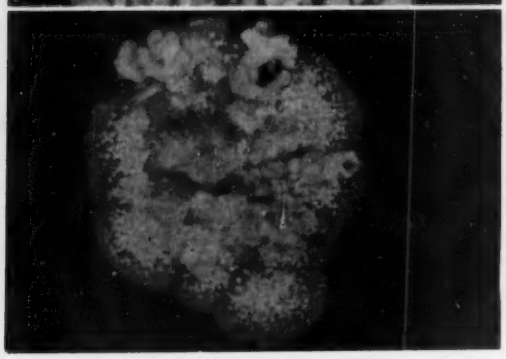
CLINICAL:



Chronic pulmonary or systemic disease characterized by visceral granulomatous lesions.

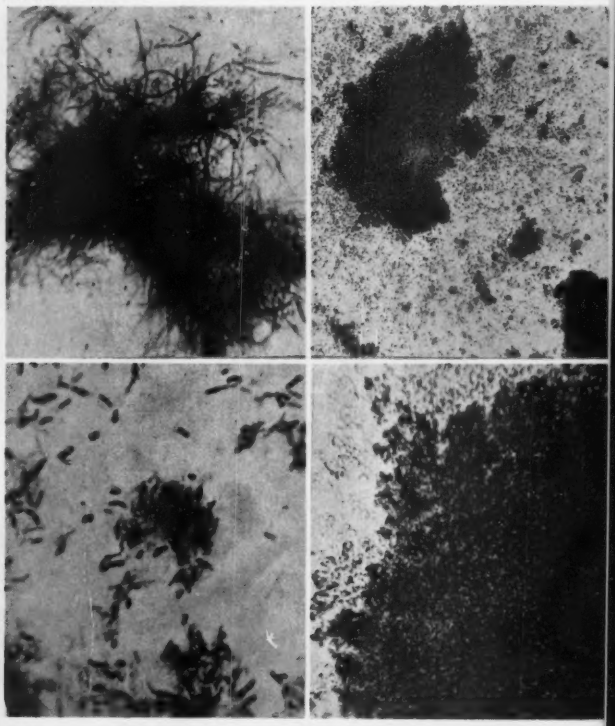
CULTURES:





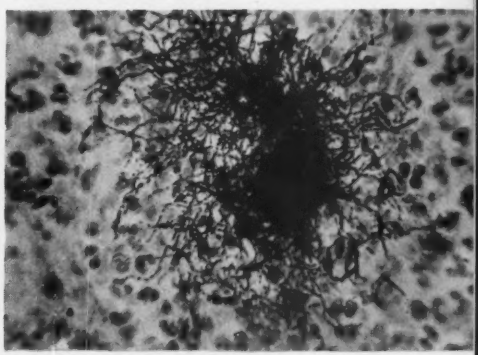
Colony: Sabouraud's medium: Glabrous, irregular, folded, raised. May be granular or powdery. Varies from white to yellow-tan. Microscopic: Delicate branched intertwining filaments. Gram positive. Acid fast.

MICROSCOPIC EXAMINATION:



Direct: Intertwining branching mycelial fragments (bacteria-like). Gram positive. No clubs formed on ends of hyphae. Nocardia asteroides is acid fast.

HISTOPATHOLOGY:



Granuloma. Branching filaments. Gram positive, may be acid fast.

TREATMENT:

Penicillin; sulfadiazine; chlortetracycline.

DISTRIBUTION: World wide.

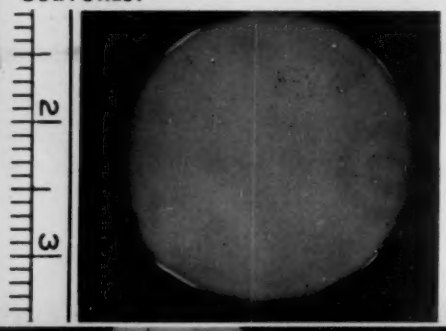
CRYPTOCOCCOSIS

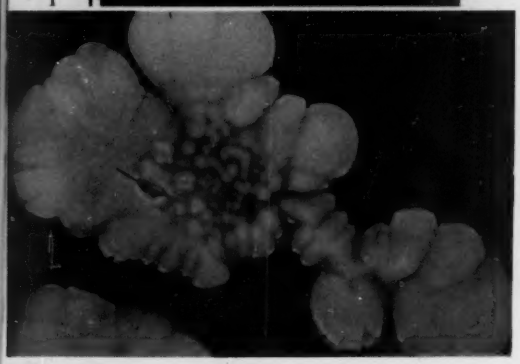
ETIOLOGIC AGENT:
Cryptococcus neoformans.

CLINICAL:

Subacute or chronic infection involving lungs, skin, brain meninges, and other organs.

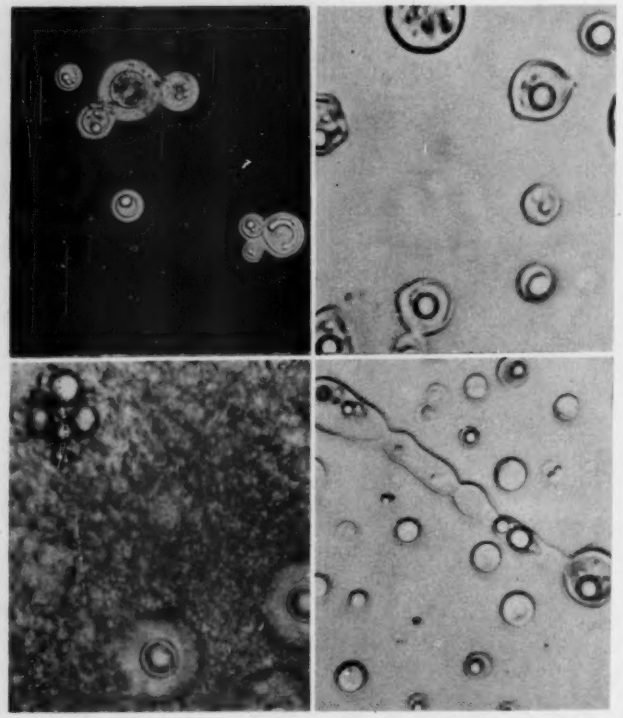
CULTURES:





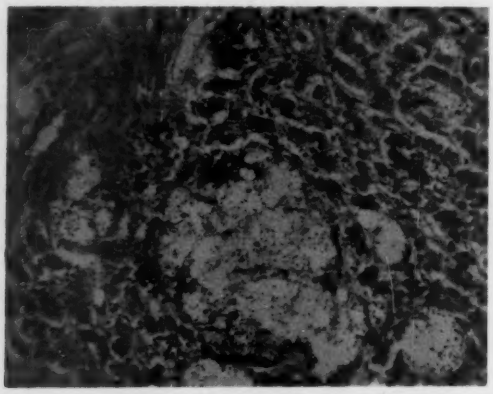
Colony:
Sabouraud's medium: Colonies white, cream to brown, yeast-like at all temperatures.
Littman's oxgall medium: Yeast-like, light purple; surface moist; shiny; center heaped.
Microscopic: Budding cells and occasional organisms with short germ tubes. May or may not have capsule. Older cultures show only budding forms—capsule prominent.

MICROSCOPIC EXAMINATION:



Direct: Thin walled, ovoid to spherical, single or budding yeast-like organisms; surrounded by wide refractile gelatinous capsule best demonstrated in india ink preparation.

HISTOPATHOLOGY:



Chronic inflammatory reaction; macrophages and giant cells may be present; often numerous single or budding organisms; cyst formation frequent.

TREATMENT: Resection. Actidione. Sulfonamides.

DISTRIBUTION: World wide.

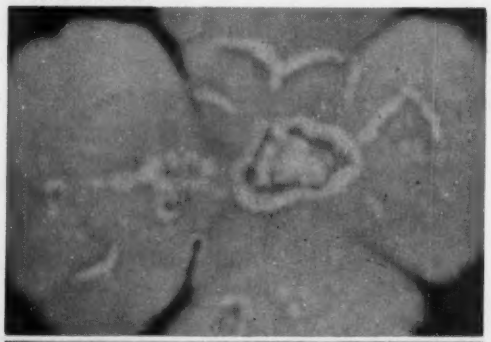
MONILIASIS

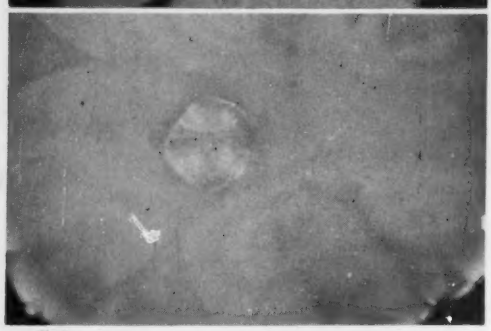
ETIOLOGIC AGENT:
Candida albicans.

CLINICAL:

Acute or subacute infections of vagina, hands, mouth, lungs; occasionally a septicemia or meningitis.

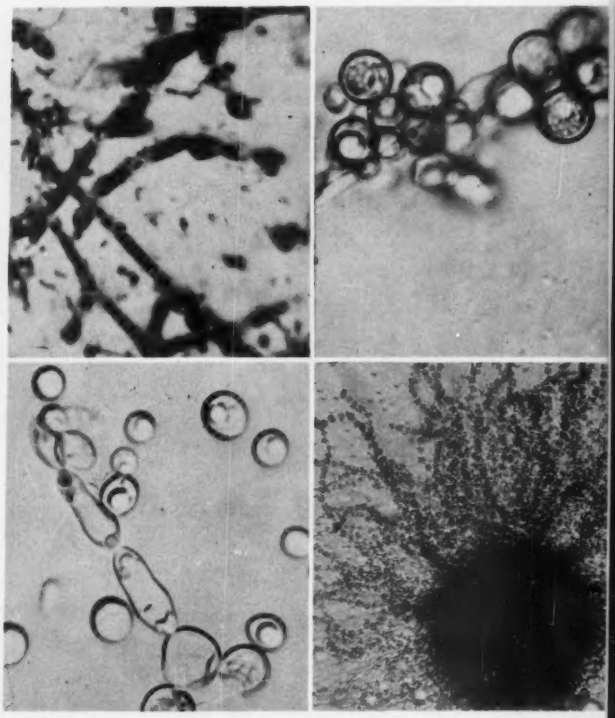
CULTURES:





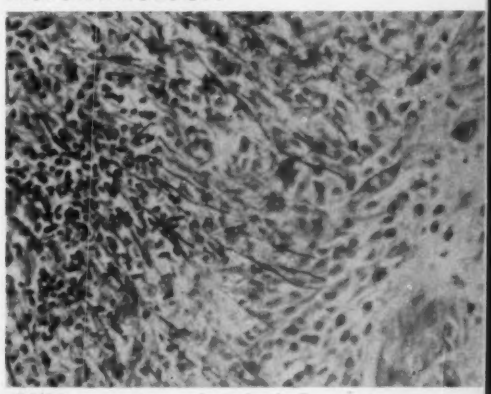
Colony:
Sabouraud's medium: Cream colored, yeast-like; distinct yeasty odor.
Littman's oxgall medium: Light purple, yeast-like, dry, waxy.
Microscopic: Small budding oval yeast-like cells. Pseudohyphae. Large chlamydospores characteristic of C. albicans on corn meal or chlamydospore agar.

MICROSCOPIC EXAMINATION:



Direct: Small oval budding yeast-like cells—occasional pseudohyphae.

HISTOPATHOLOGY:



Mild to severe chronic inflammatory reaction.
Round or oval, single or budding organisms and pseudomycelial fragments.

TREATMENT:

Gentian violet for cutaneous lesions. Alkaline douches for vaginitis. Iodides. $KMnO_4$ soaks, etc.

DISTRIBUTION: World wide.

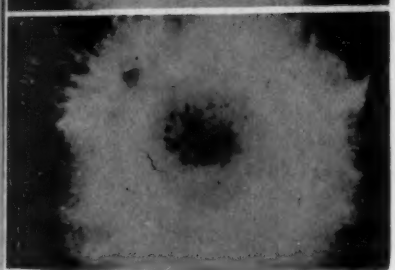
NORTH AMERICAN BLASTOMYCOSIS

ETIOLOGIC AGENT:
Blastomyces dermatitidis.

CLINICAL:

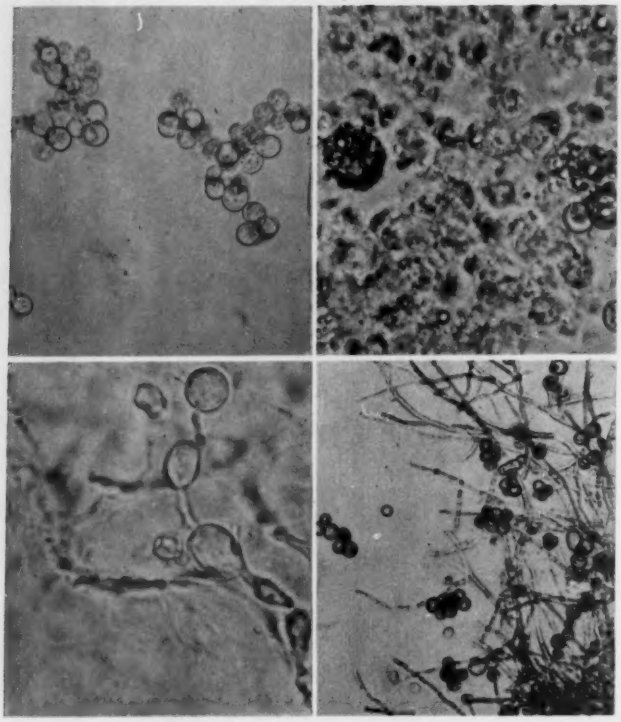
Chronic infection—granulomatous and suppurative. Mainly in skin, lungs, and bones.

CULTURES:



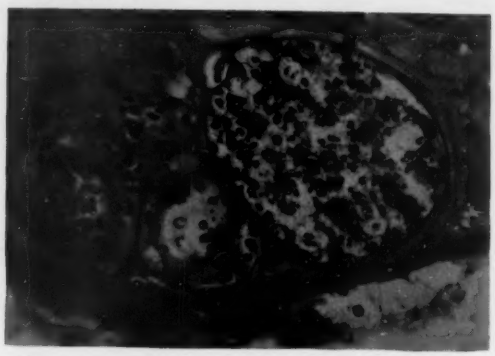
Colony:
Sabouraud's medium: Filamentous, white at 20 C. Yeast-like, white at 37 C.
Littman's oxgall medium: Umbonate with isolated tufts of mycelium, slightly furrowed, light purple at 20 C. Yeast-like purple at 37 C.
Microscopic: Septate hyphae with single small conidia. At 37 C. cells are double contoured and yeast-like with single buds from parent cell.

MICROSCOPIC EXAMINATION:



Direct: Budding cells—thick double wall. Refractile. Single buds. No hyphae present.

HISTOLOGY:



Granulomatous lesions in skin and viscera containing double-walled single and budding organisms.

TREATMENT:

Stilbamidine (i. v.). Surgical resection. X-rays. Vaccines.

DISTRIBUTION: United States, Canada, and England.

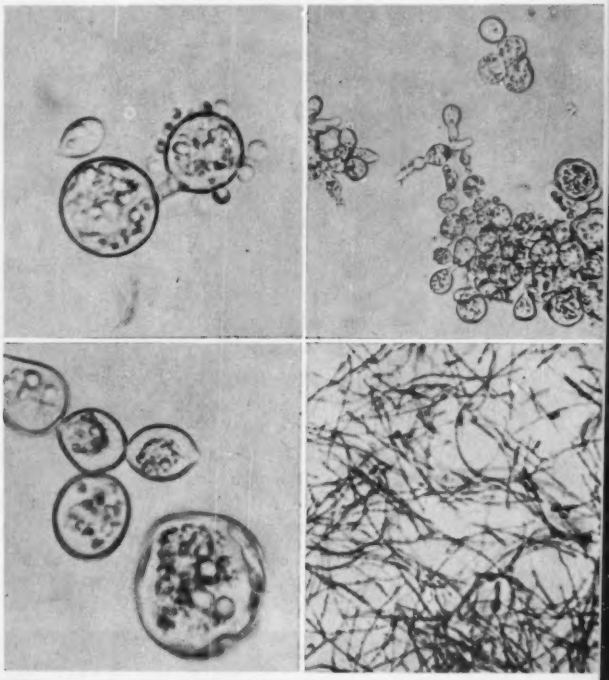
SOUTH AMERICAN BLASTOMYCOSIS

ETIOLOGIC AGENT:
Blastomyces brasiliensis.

CLINICAL:

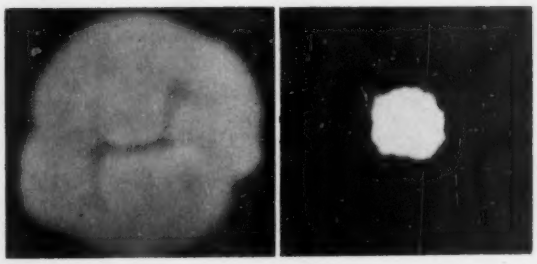
Chronic granulomatous lesions of skin, mucous membranes, lymph nodes, and internal organs.

MICROSCOPIC EXAMINATION:



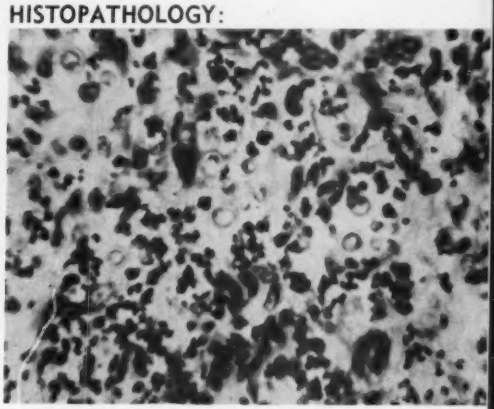
Direct: Single and multiple budding thick-walled yeast-like cells, 10-60 μ in diameter. Single cells similar to Blastomyces dermatitidis.

CULTURES:



Colony:
Sabouraud's medium: Filamentous, white at 20 C. Yeast-like, cream to white at 37 C.
Littman's oxgall medium: Slow-growing, capitate, furrowed, fuzzy, absorbs dye from medium. Yeast-like light purple at 37 C.
Microscopic: Septate hyphae with small single conidia at 20 C. Parent cell has multiple buds in yeast-like colony at 37 C.

HISTOPATHOLOGY:



Granulomatous reaction with giant cells in all tissue. Organisms present may be single or multiple and yeast-like; multiple budding organisms are characteristic.

TREATMENT: Sulfonamides. Iodides. Vaccine.

DISTRIBUTION: South America.

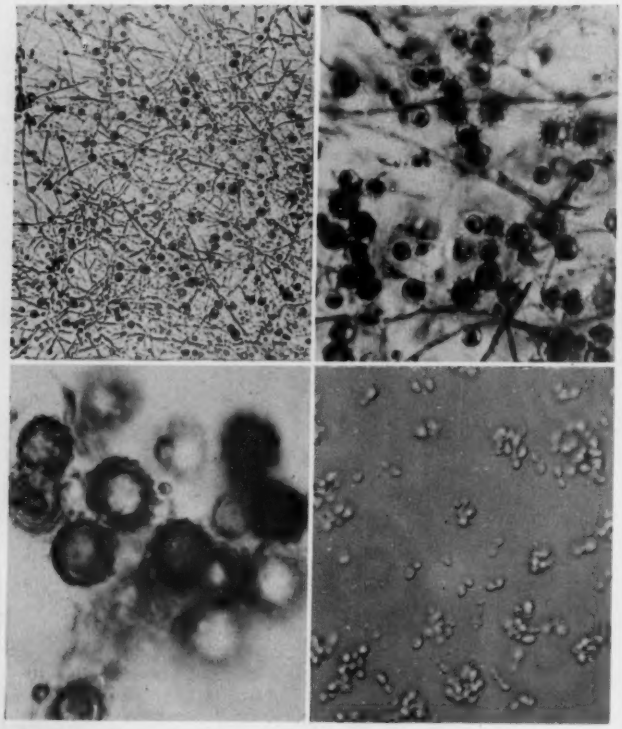
HISTOPLASMOSIS

ETIOLOGIC AGENT:
Histoplasma capsulatum.

CLINICAL:

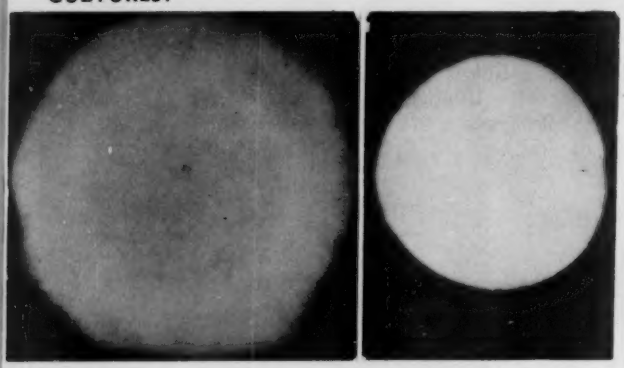
May be asymptomatic pulmonary, symptomatic pulmonary, localized, or disseminated (nonfatal or fatal). Severe infection characterized by emaciation, leukopenia, anemia, and irregular pyrexia. Frequent lymphadenopathy, splenomegaly, hepatomegaly, and ulceration of naso-oral-pharyngeal cavities and intestines.

MICROSCOPIC EXAMINATION:



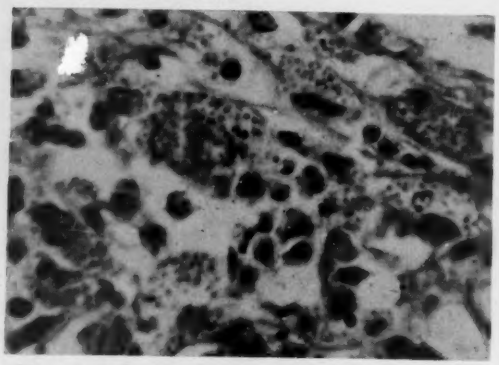
Direct: Small (1-5 μ) oval yeast-like cells in macrophages or other reticulo-endothelial cells of bone marrow, lymph nodes, spleen, liver, blood, etc.

CULTURES:



Colony:
Sabouraud's medium: Cottony white aerial mycelium at 20 C. is tan and yeast-like.
Littman's oxgall medium: Slow growing, capitate, furrowed, white to purple at 20 C.; light purple and yeast-like at 37 C.
Microscopic: Branching septate hyphae with lateral or sessile, round or oval conidia. Old colonies have characteristic round to pyriform tuberculate chlamydospores (7-15 μ). At 37 C. organisms are small, round or oval, budding yeast-like cells.

HISTOPATHOLOGY:



Chronic inflammatory reaction. Small, round or oval, single or budding organisms in macrophages, giant cells or reticulo-endothelial cells.

DISTRIBUTION:

Western Hemisphere. England. South Africa. Java.

TREATMENT:

Symptomatic therapy, surgical excision, quinacrine, ethyl vanillate, and promine.

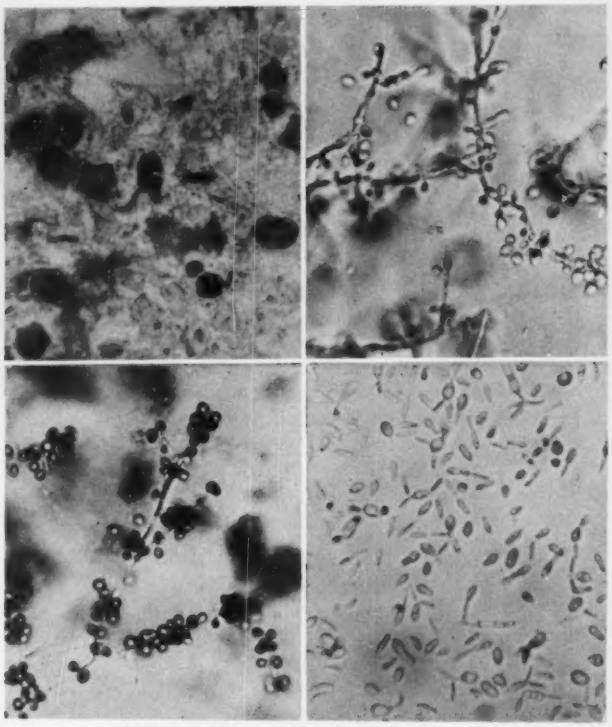
SPOROTRICHOSIS

ETIOLOGIC AGENT:
Sporotrichum schenckii.

CLINICAL:

Chronic infection with nodular lesions of lymph nodes, skin, or subcutaneous tissues, which soften and break down to form indolent ulcers. Occasionally disseminated form—acute and rapidly fulminating.

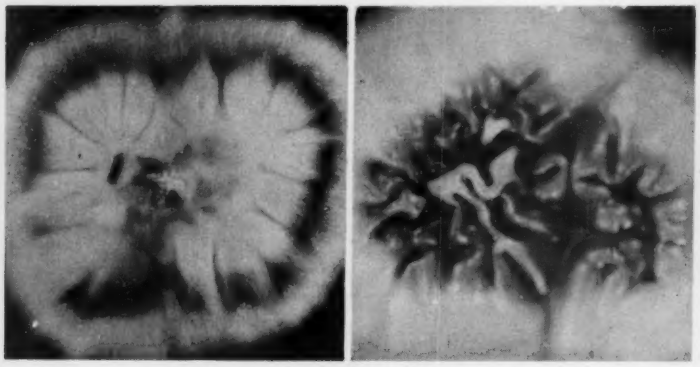
MICROSCOPIC EXAMINATION:



Direct: Gram-positive, cigar-shaped bodies within polys or giant cells. Very difficult to find. Culture necessary for diagnosis.

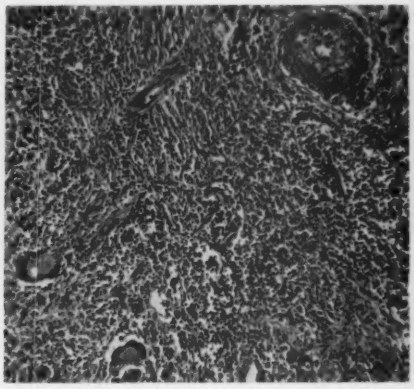
CULTURES:

Colony:
Sabouraud's medium: Small, flat, or umbonate, no aerial mycelia. Later moist wrinkled, and membranous. Color cream to white, darkens brown to black with age. Yeast-like and cream colored at 37 C.
Littman's oxgall medium: Small, corrugated; center dry, deep purple.



Periphery finely furrowed, moist, and light purple. Yeast-like and light purple at 37 C.
Microscopic:
Branching septate hyphae bearing pyriform to oval conidia in clusters from lateral branches.

HISTOPATHOLOGY:



Granulomatous reaction with giant cells and macrophages. Organisms: extremely difficult to demonstrate. Diagnosis: made by culture.

TREATMENT: K. I.; stilbamidine; x-ray; surgery.

DISTRIBUTION:

North America. Europe. South Africa.

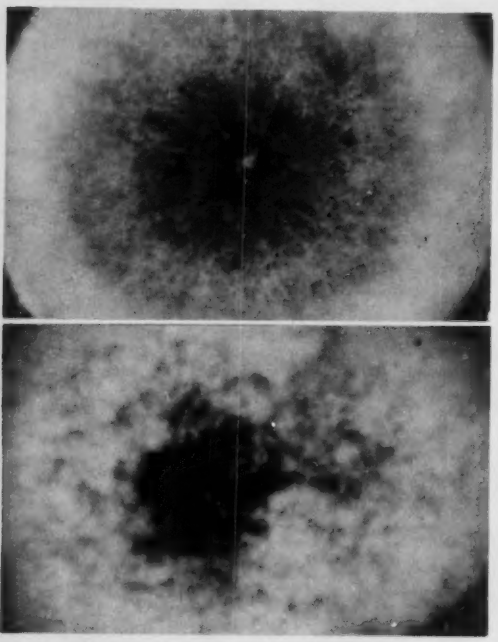
COCCIDIOIDOMYCOSIS

ETIOLOGIC AGENT:
Coccidioides immitis.

CLINICAL:

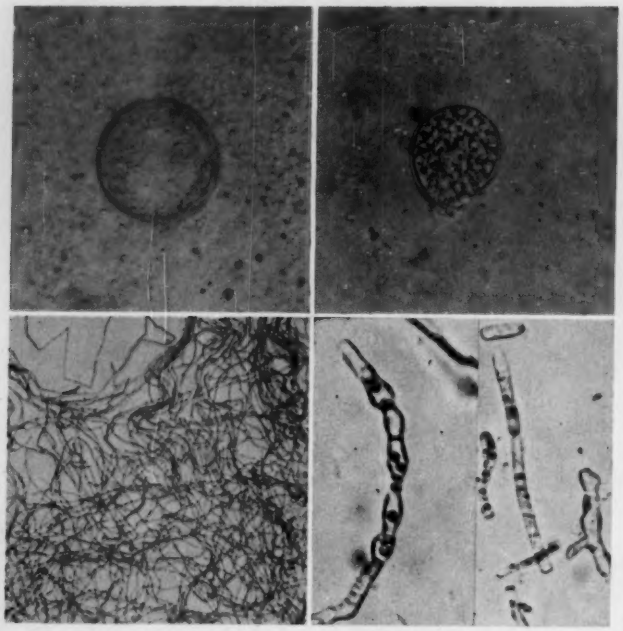
Primary—acute but benign, self-limited respiratory disease. Progressive — chronic malignant, disseminated, involving cutaneous, subcutaneous, visceral, and bone tissue. (Dark-skinned races.) Residual pulmonary —single cyst or single lobe involved.

CULTURES:



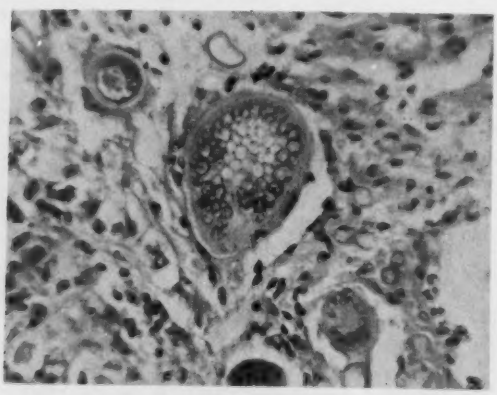
Highly infectious; extreme caution should be exercised when handling cultures.
Colony:
Sabouraud's medium: Moist—then cottony; white, then brown. Very friable, and spores spread easily.
Littman's oxgall medium: Slower growing, white, heaped and somewhat matted, then cottony. Border irregular.
Microscopic: Branching septate hyphae that break up forming thick-walled, pillow-shaped or rectangular arthrospores.

MICROSCOPIC EXAMINATION:



Direct: Nonbudding, spherical, thick-walled structure, 20-80 μ in diameter, filled with numerous endospores (2-5 μ). Immature spherules may be single nonbudding form.

HISTOPATHOLOGY:



Chronic granuloma and abscess formation with macrophages and giant cells. Large spherules filled with endospores and single spores are generally prominent.

TREATMENT: Surgical resection.

DISTRIBUTION: United States. South America?

CHROMOMYCOSIS

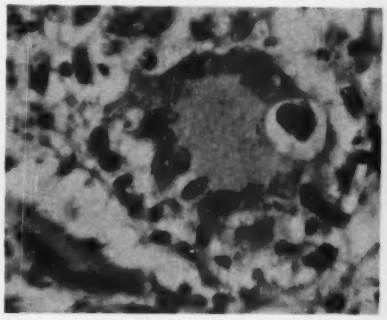
ETIOLOGIC AGENTS:

(1) Phialophora verrucosa; (2) Hormodendrum pedrosoi; (3) Hormodendrum compactum; (4) Hormodendrum sp.; (5) Cladosporium sp.

CLINICAL:

Warty cutaneous nodules; slow-growing, papillomatous vegetations which may or may not ulcerate. May occur on hands, ear, neck, chest, shoulders, or buttocks, but generally confined to head and extremities. Occasionally brain abscesses.

HISTOPATHOLOGY:

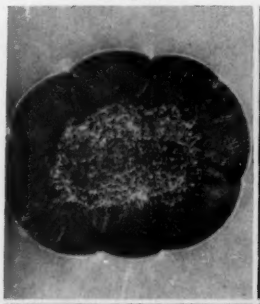
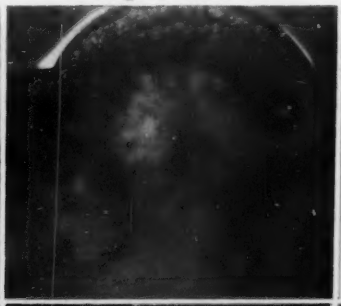
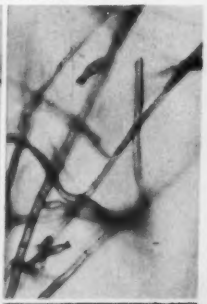
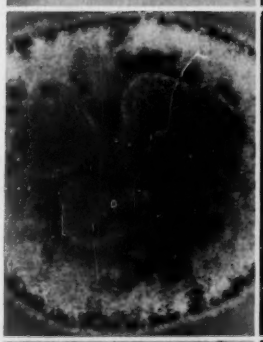
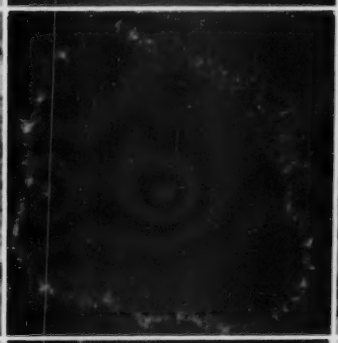
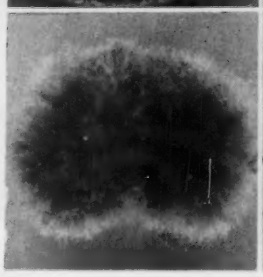


DIRECT MICROSCOPIC EXAMINATION:

Organisms small, single or clustered, round, thick-walled, brown bodies. Multiply by fission or splitting. Cultures necessary for identification of species.

Granuloma formation with numerous giant cells. Dark brown, single or clustered, round or oval organisms showing division by fission. May be located in giant cells or surrounded by macrophages.

CULTURES:

	Sabouraud's Medium	Littman's Oxgall Medium	Microscopic Characteristics	
Phialophora verrucosa:				
Hormodendrum pedrosoi:				
Hormodendrum compactum:				

TREATMENT:

Surgical excision. Cauterization.
Iodides.

DISTRIBUTION: World wide.

DERMATOMYCOSIS

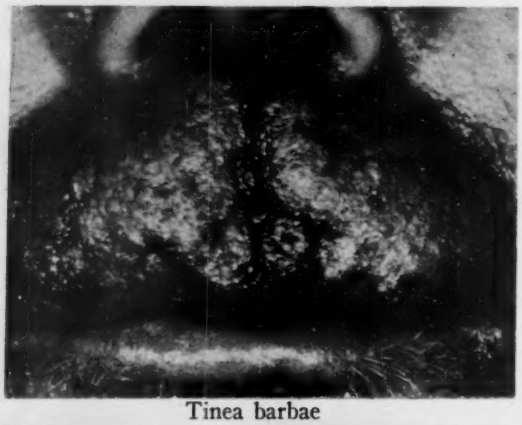
ETIOLOGIC AGENTS:

Trichophyton sp., Microsporum sp., and Epidermophyton sp. (See following two panels.)

CLINICAL DISEASE:

Chronic lesions of skin, nails and hairs varying from simple scaling to deep granulomatous and kerion-like tumors.

Tinea capitis



Tinea barbae

Tinea corporis

Dermatophytosis of Hands and Feet

Tinea cruris

Tinea ungium

HISTOPATHOLOGY:

Septate mycelia growing in epidermis and adjacent structures often associated with varying amounts of secondary bacterial infection.

TREATMENT:

Fungicides. Epilation. X-rays. Personal hygiene.

DISTRIBUTION: World wide.

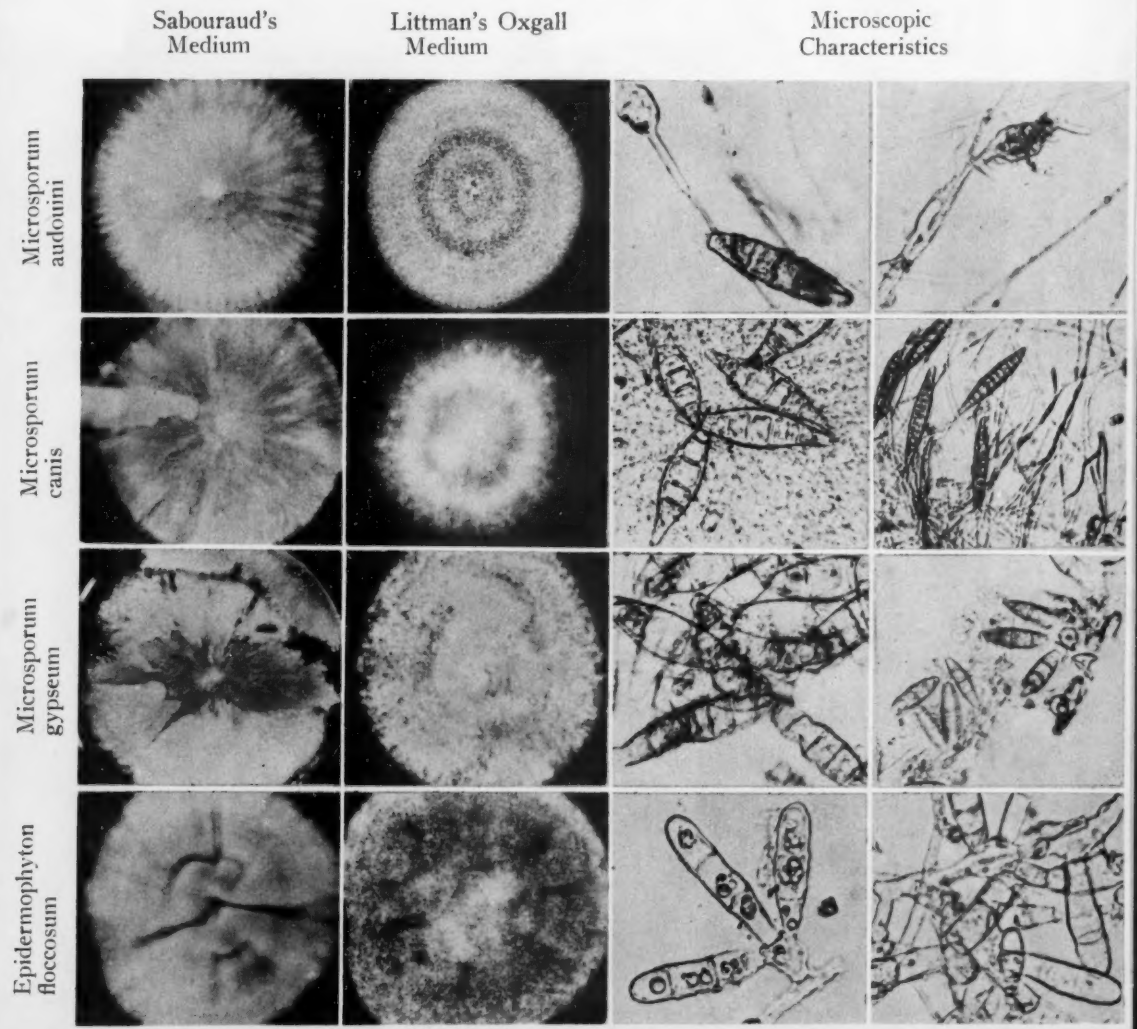
EPIDERMOPHYTON & MICROSPORUM SP.

ETIOLOGIC AGENTS:
Microsporum audouini; Microsporum canis; Microsporum gypseum; Epidermophyton floccosum.

CLINICAL DISEASE:
Often the causative agent in tinea capitis and tinea cruris and occasionally in the other dermatomycoses.

DIRECT MICROSCOPIC EXAMINATION:
Fragments of mycelia and arthrospores in scales of epidermis and hairs. Identification of etiologic agent depends on cultural characteristics.

CULTURES:



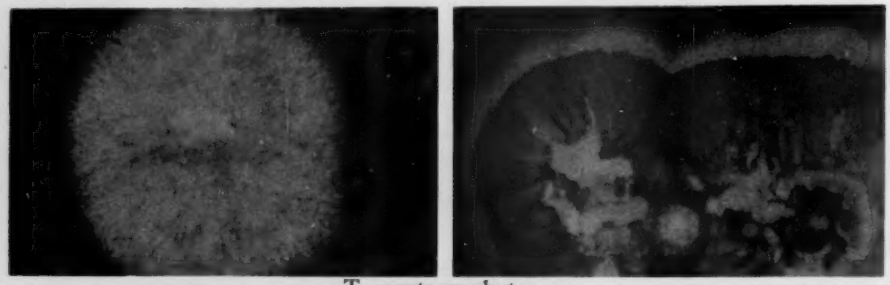
DERMATOMYCOSIS

ETIOLOGIC AGENT:
Trichophyton sp.

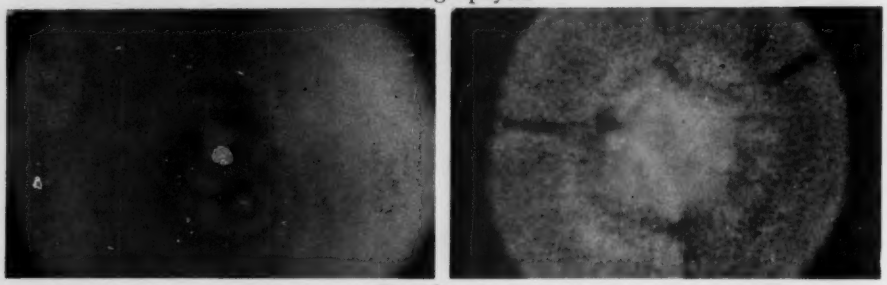
Cultural Characteristics

CULTURES:

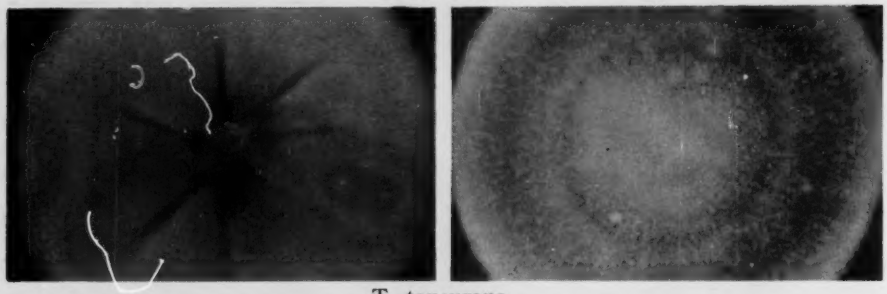
Sabouraud's Medium | Littman's Oxgall Medium



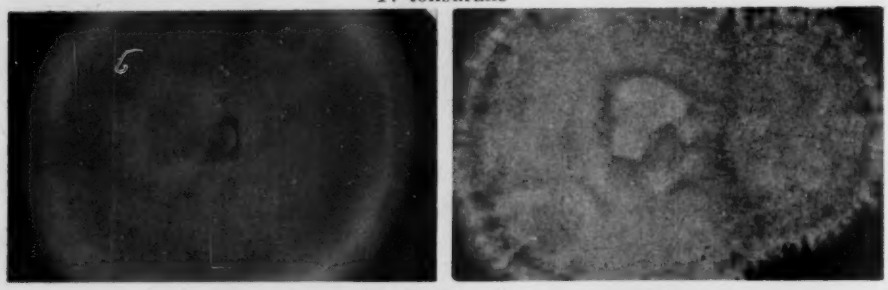
T. mentagrophytes



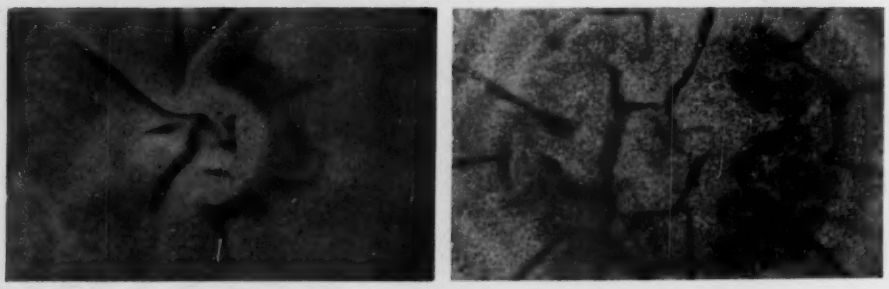
T. rubrum



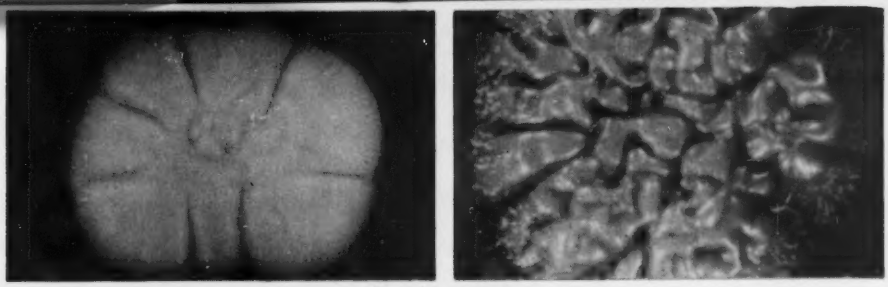
T. tonsurans



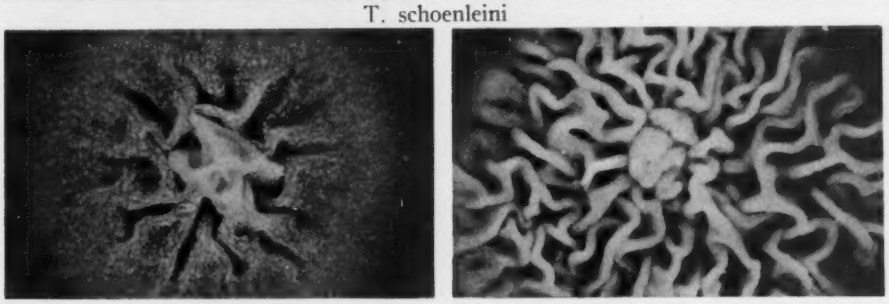
T. sabouraudi



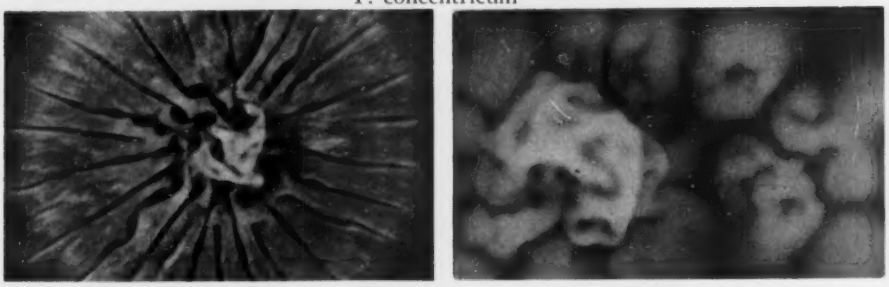
T. sulfureum



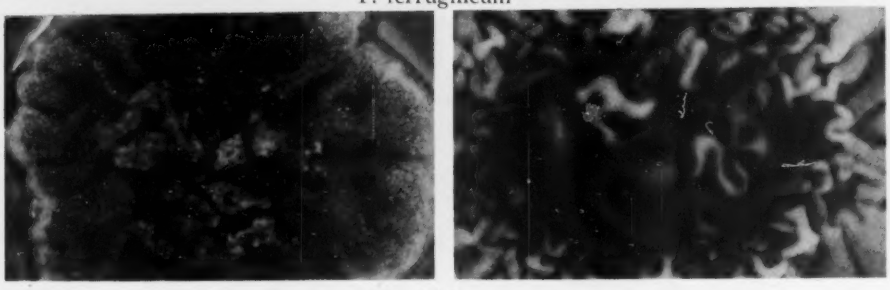
T. schoenleini



T. concentricum



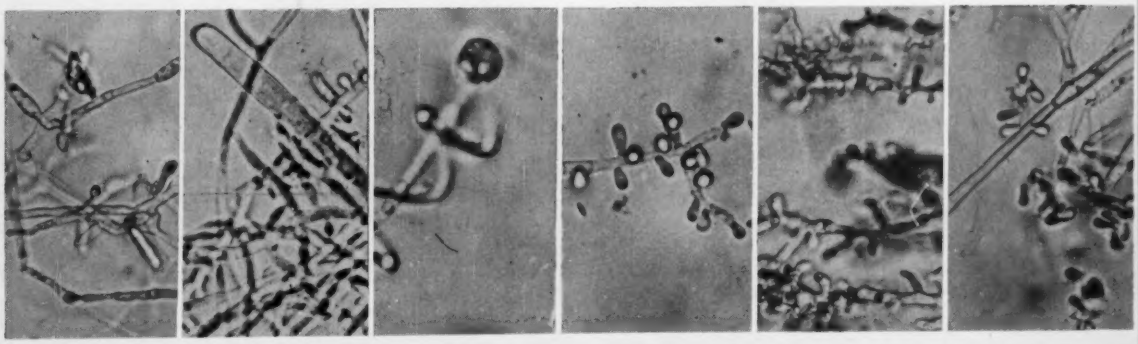
T. ferrugineum



T. violaceum

DIRECT MICROSCOPIC EXAMINATION:

Fragments of septate mycelia and arthrospores in scales of epidermis, fragments of nails and hairs. Identification of etiologic agent depends on cultural characteristics.



OCCASIONAL PATHOGENS

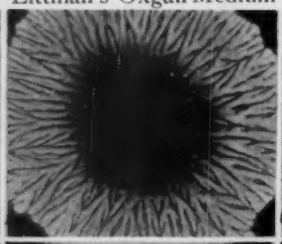
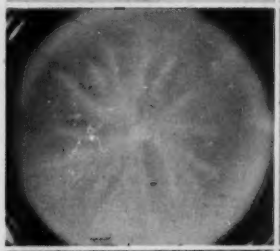
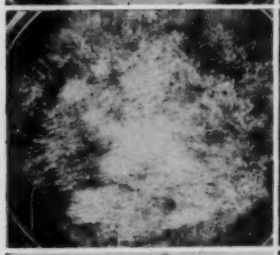
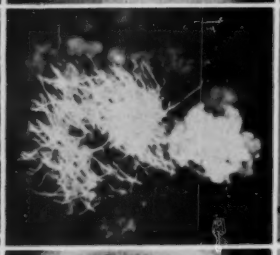
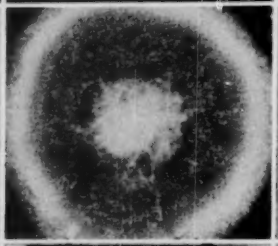
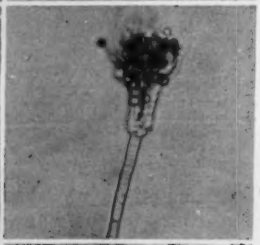
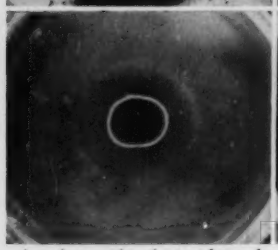
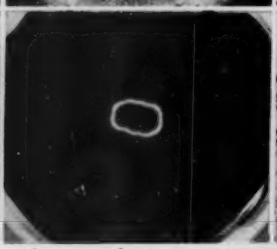
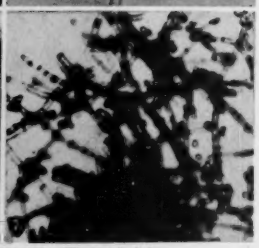
ETIOLOGICAL AGENTS: Aspergillus sp.; Geotrichum sp.; Mucor sp.; Penicillium sp.; Hormodendrum sp.

CLINICAL DISEASES: Occasionally lesions like otomycosis, pneumonia, diarrhea, and brain abscesses are produced by these fungi generally considered to be contaminants. No other etiologic agents can be isolated.

DIRECT MICROSCOPIC EXAMINATION:

The material examined contains septate hyphae and occasional spores. Mucor sp. mycelia are non-septate. Material must be cultured for specific diagnosis.

CULTURES:

	Sabouraud's Medium	Littman's Oxgall Medium	Microscopic Characteristics
Aspergillus sp.			
Geotrichum sp.			
Mucor sp.			
Penicillium sp.			
Hormodendrum sp.			

HISTOPATHOLOGY: Reaction in tissue is that of a chronic granuloma containing fragments of mycelia and occasional spores. Material must be cultured for specific identification.

TREATMENT: Fungicides.
Surgical excision.
Symptomatic care.

DISTRIBUTION: World wide.

Correspondence

EVIDENCE FOR RELATIONSHIP BETWEEN SODIUM (CHLORIDE) INTAKE AND HUMAN ESSENTIAL HYPERTENSION

To the Editor:—I wish to call your attention to a few statements made by Dahl and Love in relation to the frequency of hypertension among "low, average, and high" salt intaking groups of people (October, 1954, issue of the ARCHIVES), viz.:

(*a*) While hypertension (in its essential form) among certain "primitive" ethnic groups could owe its rarity to their low salt intake, such an explanation can hardly hold for the Quechua and Aymara Indians of the South American Altiplano, among whom I practiced for many, many years; their salt intake is rather high, but their percentage of hypertensives (and, curiously enough, of gastric carcinoma, too) is very low. On the other hand, we should not forget that the Eskimos ingest a highly (albeit intrinsically) salted food: their staple food is represented by sea fish, whale, etc.—all animals with a high amount of salt in their tissues, as has been shown some time ago by the father of paleochemistry, Bigaart (in Brussels)—and yet they rarely develop hypertension.

(*b*) Moreover, while I admit that nothing is more difficult than to define the upper limit of "normal" blood pressure, I believe that one can hardly doubt the value of the work of Master and his associates in "revaluation of boundaries" in this matter. Be that as it may be, I do not see how an occasional (or even frequent) reading of 140/90 could be considered even as prima facie evidence of hypertension in a middle-aged person, and yet these are the criteria the authors apply in their otherwise highly interesting and thought-provoking article.

In résumé, I consider that the problems touched upon by the above-named authors need far more (and a rather different) investigation.

MARDOQUEO I. SALOMON, M.D.
1450 Bryant Ave., Bronx, N. Y.

To the Editor:—Thank you for the letter from Dr. Salomon. I should prefer to let more facts and time demonstrate whether or not the proposed hypothesis is valid. If it is wrong, no arguments would change that fact.

Relative to Point *a* in Dr. Salomon's letter, I have no data on the salt intake of the South American tribes he names but would be interested to have some precise information on this subject. Unless they have some process for adding salt to their native foods, however, I suspect that their actual average intake is not very high, compared with civilized societies. This is true at least for the primitives on whom I have data. Natural foods are either animal flesh or plants, and their derivatives. By and large, the flesh that is eaten is muscle, and muscle is a high potassium (not sodium) food. Furthermore, animals apparently differ very little in this respect: quoting from a recent review of water and electrolyte metabolism, "The concentration of electrolytes is remarkably constant throughout the animal kingdom from frogs, fish, and fowl to dolphins and polar bears" (Manery, J. F.; *Physiol. Rev.* **34**:379, 1954). Plants, it is true, will have a variable Na content dependent upon that of the soil in which they are grown (Miller, E. C.: Plant Physiology, Ed. 2, New York, McGraw-Hill Book Company, Inc., 1938, p. 288). The magnitude of change, however, is not enough to yield highly salted products and thereby lead to a high Na intake. In fact, we have not yet found natural foods with a truly high salt content which are taken in large quantities. Such situations may well exist and your readers would render a service by so informing me. Eskimos do not have a high salt diet. Ehrström, who studied them in 1948-1949 (*Acta. med. scandinav.* **140**:416, 1951) estimated the diets of the North Greenland Eskimos to contain 3 to 5 gm. NaCl/day and these were not true primitives. Primitive Eskimos fell into two broad groups relative to their diets: the coastal and the inland tribes. The second group subsisted predominantly upon caribou, lake fish, birds—none of which would lead to a high Na intake unless salt were added in preparation: these foods are primarily muscle. The coastal tribes largely ate sea fish, whale, and seal, and, from the last two, blubber made up their great source of calories. Fat is a very low Na source. In the absence of fat or other food, I suppose an adult Eskimo might possibly eat 3 to 5 kg. of meat a day and, with their feast or famine mores, perhaps more for short periods. If an average value of 60 mg. Na/100 gm. (Bills, C. F., and others: Sodium and Potassium in Foods and Waters, *J. Am.*

Dietet. A. **25**:304, 1949) is assigned to these muscle foods (certain organs, e. g., kidney, are higher), this would amount to 1,800 to 3,000 mg. Na/day, a level well below the average American diet, and I doubt if this would be the sole food for a life time.

Relative to Point *b*, I would say that at whatever level above 140/90 one chooses to call blood pressure high, those with such pressures in this series would fall into the average and high Na intakes and not the low.

Statistics cannot ever prove the truth of anything, but only indicate the probability thereof. The elementary statistical analysis used in the paper indicated that the distribution as found could occur by chance about once in 60 times. While this is significant for biological studies, it does not constitute proof.

In conclusion, the concept which we proposed regarding the central role of Na in essential hypertension has been regarded as a working hypothesis. If it suggests experiments to ourselves or others which aid in the elucidation of this disease, the concept will have been useful. As one engaged in full-time research on this problem, I should be delighted to have suggestions from Dr. Salomon or others for further investigations.

LEWIS K. DAHL, M.D.

MANAGEMENT OF CONGESTIVE FAILURE

To the Editor:—The paper "Management of Congestive Failure" by D. A. Rytand, M.D., is too misleading in respect to the use of oxygen in cardiac failure to allow it to stand without question.

Oxygen therapy is among the most valuable agents in the treatment of chronic cor pulmonale. When administered in small and gradually increased oxygen concentrations, the adverse effects of abrupt inhalation of high concentrations are generally prevented, as has been repeatedly emphasized since 1938. The use of 100% oxygen has not been advocated by any responsible investigator for the treatment of pulmonary emphysema, with or without cor pulmonale.

The value of 40 to 50% oxygen in the treatment of left ventricular failure in cases of hypertensive and coronary artery disease was also established in the studies of Richards and the author, in which it was shown that relief of dyspnea was accompanied by a decrease in the minute volume of ventilation, an increase in CO_2 in the blood, and the inauguration of a diuresis, accompanied by a high urinary output of chlorides. In this type of case coma does not occur as consequence of administration of 40 to 50% oxygen by catheter or oxygen tent. The homostatic basis of the increased arterial CO_2 in the expired air is an integral part of the mechanism which resulted in the relief of dyspnea and the restoration of cardiorespiratory compensation.

In reference to the statement, "The customary levels of 6 to 8 liters per minute of oxygen" used in the tent; I do not remember that 6 liters per minute was ever prescribed in a tent without the use of soda lime. For many years 10 liters per minute was the minimum flow and 12 liters per minute has been suggested as the proper flow of oxygen for a tent. A concentration of 50% oxygen can not possibly be obtained at 6 to 8 liters per minute unless at the expense of undesirable levels of carbon dioxide. The 10 to 12 liters per minute flows are required both to obtain adequate oxygen concentrations and low CO_2 percentages in the atmosphere in the tent.

The reader of this paper would indeed be enlightened by consulting the studies in this field; those which bear on the physiological and clinical effects of oxygen therapy in right and left heart failure, especially in respect to the diffusion of oxygen and carbon dioxide, are noted below.

1. Barach, A. L., and Richards, D. W.: Effects of Treatment with Oxygen on Cardiac Failure, Arch. Int. Med. **48**:325, 1931.

2. Richards, D. W., Jr., and Barach, A. L.: Prolonged Residence in High Oxygen Atmosphere: Effects on Normal Individuals and on Patients with Chronic Cardiac and Pulmonary Insufficiency, Quart. J. Med. **3**:437, 1934.

3. Barach, A. L.: Physiological Methods in the Diagnosis and Treatment of Asthma and Emphysema, Ann. Int. Med. **12**:454, 1938.

4. Barach, A. L.: Physiologic Therapy in Respiratory Diseases, Philadelphia, J. B. Lippincott Company, 1948.

5. Richards, D. W., Jr.: Cardiac Failure, Bull. New York Acad. Med. **26**:384, 1950.

6. Levy, R. L.: Oxygen in Cardiac Infarction, Bull. New York Acad. Med. **26**:394, 1950.

ALVAN L. BARACH, M.D.

News and Comment

ANNOUNCEMENTS

M. D. Anderson Symposium.—The Ninth Annual M. D. Anderson Symposium on Fundamental Cancer Research will be held March 10, 11, and 12, 1955, at The University of Texas M. D. Anderson Hospital and Tumor Institute, in the Texas Medical Center, Houston.

The first day of the program will be a review of the current research projects at the hospital. This will be followed in the evening by the first formal gathering for the Symposium: a discussion of the Epidemiology of Cancer by Miss Eleanor Macdonald, followed by a presentation on Experimental Design by Dr. John Fertig, Professor of Columbia University Medical School, Department of Statistics.

The second day of the Symposium will be devoted to histochemistry. Dr. George Gomori, of the University of Chicago, will be the Chairman of this program, and he has chosen six national figures as speakers, who will present this day's activity.

The final day of the Symposium will be devoted to presentations reflecting current cancer research in the Southwest, for which Dr. A. Clark Griffin, of M. D. Anderson Hospital, has assembled an interesting series of papers.

The Bertner Award will be made the evening of March 11, at a Banquet held at the Doctor's Club, in the Library Building of the Texas Medical Center, Houston.

Clinical Hematology Course.—A three-day continuation course in clinical hematology will be presented at Tulane University, beginning March 23, 1955. Dr. C. V. Moore, Dean and Professor of Medicine at Washington University, has accepted an invitation to be guest speaker. Registration is now open to all physicians but will be closed March 1, 1955.

The program will be built around actual cases insofar as possible and will include discussion of the anemias, leukemias and lymphomas, polycythemia, purpura, problems of blood transfusion, and blood coagulation.

U. S. Civil Service Trainee Positions.—The U. S. Civil Service Commission has announced that applications are now being accepted for Medical Officer for filling the following trainee positions in St. Elizabeths Hospital, Washington, D. C.: rotating intern, $2,800 a year, and resident-in-training in psychiatry and in neurology, $3,400 to $4,200 a year. Appointments will be open July 1, 1955.

Applicants for the intern positions must be fourth-year students in an approved medical school. For the resident positions, applicants must be graduates from an approved medical school with the degree of doctor of medicine and in addition must have completed a full year's internship or now be serving such internship. No written test is required. The age limit of 35 years will be waived for persons entitled to veteran preference. Full details concerning the requirements is given in examination announcement No. 429 (B).

Applications will be accepted until further notice by the Board of Civil Service Examiners, St. Elizabeths Hospital, Washington 20, D. C. Further information and application forms may be obtained from most post offices or from the U. S. Civil Service Commission, Washington 25, D. C.

Expansion and Reorganization of Commissioned Reserve, P. H. S.—A major expansion and reorganization of the Commissioned Reserve of the Public Health Service, Department of Health, Education, and Welfare, as a national defense measure has been announced by Surgeon General Leonard A. Scheele. The Service expects to commission an additional 2,000 reserve officers by June 30, 1955, and present plans call for the commissioning of another 3,000 officers during the 1955-1956 fiscal year.

The Service has been assigned extensive new defense responsibilities as the result of a delegation by the Federal Civil Defense Administration to the Department of Health, Education, and Welfare, recently approved by the President. In addition to building up the Commissioned Reserve to emergency strength, the Service is stepping up research in disaster health problems and is developing a program to reinforce State and local health departments in time of national crisis.

In strengthening the Commissioned Reserve, the Service has two fundamental objectives: (1) Effective emergency utilization of professional personnel with training and experience in public health and (2) augmenting these forces with physicians and other professional people not normally working in the field of public health.

Dr. Scheele said that an officer of the emergency reserve would be called to active duty without his consent only in the event of a national emergency publicly recognized as requiring such action and that an officer of the emergency reserve already performing important health functions would not be called for service in another area unless the situation in that area clearly justified it. Officers in the emergency reserve may request active duty at any time and will be considered for available assignments.

The emphasis initially will be on the commissioning of physicians, dentists, santitary engineers, and nurses, particularly physicians, the Service said.

In the near future the Public Health Service expects to start training officers of the emergency reserve in the health problems associated with atomic, biological, and chemical warfare and other national emergencies. As the expansion goes forward, the Service hopes to train all reserve officers who can arrange to be away from their regular work for brief periods.

Information Exchange in Chemotherapy of Cancer.—To assist scientists engaged in studies on the chemotherapy of cancer, a program for wide exchange of information in this field of medical research has been established by the Committee on Chemotherapy of the National Advisory Cancer Council in cooperation with the National Cancer Institute, the American Cancer Society, and the Damon Runyon Fund. All investigators interested in cancer chemotherapy are invited to take part in the program. Chairman of the committee is Dr. Sidney Farber, Director of the Children's Cancer Research Center, Boston.

A variety of activities will be developed through the program. Among them are the following:

Issuance of a periodic compilation of informal reports on current research in cancer chemotherapy.

Formal conferences and symposia on cancer chemotherapy.

Compilation and issuance of a bibliography of cancer chemotherapy literature covering the period from 1946 through 1954.

Provision of opportunities for individuals and small groups to meet informally in various parts of the country for discussions of interinstitutional studies, of standards for evaluating chemical agents, of difficulties in this research area, of potentially useful agents, and of other topics the conferees consider pertinent.

In addition, the committee plans to bring to the attention of investigators chemical agents which may be of interest to them and to assist them in obtaining the chemicals in sufficient quantity for evaluation.

Investigators who wish to take part in any of the activities of the program are invited to write to Dr. Gordon Segar, Secretary, Cancer Chemotherapy Committee, National Cancer Institute, Bethesda 14, Md.

Course in Internal Medicine.—The University of Minnesota announces a continuation course in Recent Advances in Internal Medicine for internists, which will be presented at the Center for Continuation Study Feb. 14-16, 1955. This year's course will deal with various aspects of hematology, cardiology, endocrinology, and respiratory physiology. The course will be presented under the direction of Dr. C. J. Watson, Professor and Director, Department of Medicine. Lodging accommodations will be available at the Center for Continuation Study, as usual.

Books

The Thyroid: A Physiological, Pathological, Clinical and Surgical Study. By Tobias Levitt. Price, $20.00. Pp. 606. E. & S. Livingstone, 16 and 17 Teviot Place, Edinburgh 1; Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1954.

This book is a long and comprehensive general review of practically all aspects of thyroid disease. Considerable space is devoted to physiology of the thyroid gland and to various pathologic conditions encountered in the management of disease of the thyroid gland. It contains many excellent colored photomicrographs and photographs of patients with different thyroid conditions.

Many of the author's conclusions, however, are largely theoretical and without adequate factual basis. This is particularly true of his concept that all forms of thyroid disease, including Hashimoto's and Riedel's thyroiditis, represent various phases in the natural course of diffuse parenchymatous hypertrophy. His statements about changes in thyroid function that occur with advancing age and at the time of the climacteric as well as his ideas regarding the relation of the thyroid gland to other endocrine glands are at considerable variance with those of most present-day thyroidologists.

The book is interesting and provocative. Unfortunately, however, it is likely to convey to the casual reader not intimately familiar with thyroid disease the impression that few if any major problems of thyroid physiology remain unsolved and that the pathogenesis of various thyroid abnormalities is no longer open to question.

Managing Your Coronary. By William A. Brams, M.D. Price, $2.95. Pp. 158. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5; Aldine House, 10-13 Bedford St., London, W.C. 2; 2083 Guy St., Montreal, 1953.

This small volume is intended for the patient and fully meets this goal. The author presents the facts on coronary disease in a direct, clear, and easy style. He leaves the impression of utter frankness without any element of alarm for even the most apprehensive type of patient. Facts on physiology, pathology, methods of diagnosis, and reasons for details of treatment are made available in an interesting, chatty, and effective manner. Throughout there is the emphasis on common sense and moderation, such as only a very experienced clinician can provide.

The chapters on the process of healing, on the program of rehabilitation, and on the modes of scientific research in the field of coronary disease are particularly well done. The problem of restriction of cholesterol in the diet is dealt with sensibly in the light of our present inadequate knowledge.

This book is to be highly recommended not only for the layman with coronary disease but for other members of the family and for the physician who has to manage the patient not only through the terrifying acute episode but through the long years ahead.

Acute Anuria: A Study Based on Renal Function Tests and Aspiration Biopsy of the Kidney. By Claus Brun. Price, D. kr. 30.00. Pp. 215. Ejnar Munksgaards Forlag, Nørregade 6, København, K, 1954.

This monograph presents a thorough discussion of the problems of acute anuria, including detailed studies on 32 patients. The first part of this monograph is devoted to a comprehensive review of the literature on toxic and ischemic types of tubular necrosis, on the pathogenesis and mechanisms involved in anuria, and on the renal-function pattern as determined by the special clearance studies. The concept of lower nephron nephrosis is appropriately criticized in the light of Oliver's recent work.

Part 2 consists of the author's detailed studies on his clinical series. In addition to the complete battery of renal-function tests there is an interesting series of renal biopsies, some of which are compared with autopsy studies on the same patients. The lesions are clearly shown to be distributed in the proximal as well as in the distal convoluted tubules. The histological changes are not specific for the etiological diagnosis of the tubular lesions.

The author recommends the usual conservative treatment for acute anuria and leans toward the use of intermittent dialysis where specifically indicated. He found that complete return to normal renal function almost always occurred within 6 to 12 months except in patients with previous intrinsic renal disease.

There is an excellent bibliography and a chapter on techniques of some of the clearance tests. This volume is a timely and interesting review of an important subject.

Pharmakologie als theoretische Grundlage einer rationellen Pharmakotherapie. By Knud O. Møller. Price, not given. Benno Schwabe & Co., Klosterberg 27, Basel 10, 1953.

This is a standard text of pharmacology of about 800 pages in German. The arrangement of the material is the usual one, with a brief introduction to the principles of pharmacologic action and chapters on disinfectants, bacteriostatic and bactericidal substances, and topically active substances. Narcotica and the pharmacology of the autonomous nervous system and the cardiovascular system follow. Other sections deal with the pharmacology of metabolism and vitamins, the hemopoietic system, electrolytes, and heavy metals. The treatment of the subject matter is thorough and clear. Physiologic relationship of pharmacologic action is gone into on many occasions. There are a fair number of references extending to 1952.

Although the book does not attain the stimulating value of the old German Meyer-Gottlieb text, it can be recommended for those who want an up-to-date text-book on pharmacology in German.

Newer Concepts of the Causes and Treatment of Diabetes Mellitus: Proceedings of the Symposium on Diabetes Sponsored by the New York Diabetes Association and Held at Memorial Hospital and The New York Academy of Sciences. Price, $2.50. Pp. 177. The National Vitamin Foundation, Inc., 15 E. 58th St., New York 22, 1954.

This series of concise papers presents in a coordinated fashion, for the benefit of the practitioner, the progress being made in biochemical and clinical investigations in the field of carbohydrate metabolism. The discussions include obesity and glycogenesis in experimental diabetes; certain endocrine aspects of carbohydrate metabolism, including the hypoglycemia factor of the pancreas; several papers relating to nutrition and diabetes, including vitamin B_{12}, and several papers concerning the clinical management of diabetes, its complications, the disease during pregnancy, the control of surgical infections, and the role of psychological disturbances. Because the fundamental research is reported in most instances with commendable clarity and brevity, the pamphlet is heartily recommended to the clinician.

Symposium on Protein Metabolism: Proceedings of the Nutrition Symposium Held at the University of Toronto, Toronto, Canada. Price, $1.50. Pp. 103. The National Vitamin Foundation, Inc., 15 E. 58th St., New York 22, 1954.

Each of the seven papers in this symposium is a well-rounded view of important aspects of protein metabolism which are now under investigation. Among the more important subjects discussed are the relations of vitamin B_6, riboflavin, and vitamin B_{12} to protein metabolism; the role of vitamins in antibody production as a measure of protein synthesis; the effects of growth hormone on protein metabolism; the amino acid requirements of man, and the use of amino acids and proteins in therapy.

Fundamentals of Otolaryngology: A Textbook of Ear, Nose and Throat Diseases. By Lawrence R. Boies, M.D. Second edition. Price, not given. Pp. 471, with 197 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1954.

The second edition of Boies' "Fundamentals of Otolaryngology" contains 471 pages of text with a complete subject index and is profusely illustrated. The arrangement of topics under regions and symptoms is useful for the student and practitioner. Primarily designed for undergraduate teaching, this textbook is also an excellent basic text for the resident who is beginning to specialize in otolaryngology as well as for the general practitioner who wishes a convenient reference work for otolaryngological problems that he encounters so frequently in general practice. There is an interesting "Introduction to Modern Otolaryngology" preceding Chapter 1,

which clearly describes the rapid changes that are occurring in this specialty with a widening of its areas and vistas. This improved second edition will continue to appeal to teachers and students as an ideal textbook for the undergraduate medical student.

Patología del Estómago Operado. Second Argentinian Congress of Gastroenterology. Price, not given. Pp. 482, with 124 illustrations. Editorial Universitaria, Paraguay 2074, Buenos Aires, 1953.

The book, entitled "Pathology of the Operated Stomach," is divided into ten chapters, as follows: I. Blood Changes, II. Physiopathology, III. Radiology, IV. Gastroscopy, V. Postoperative Pathology, VI. Late Postoperative Pathology, VII. Repercussions on Biliary Tract, VIII. Repercussions on the Endocrine System, IX. Treatment, X. Corticovisceral Pathology of the Gastrectomized Patient. The various contributors to this book are very well qualified to present their various contributions, and their presentations of the different subjects mentioned above are clear and concise and offer a practical approach in resolving the various problems encountered in the gastrectomized patient.

Serological Approaches to Studies of Protein Structure and Metabolism. Edited by William H. Cole. Price, not given. Pp. 97, with 46 illustrations. Rutgers University Press, New Brunswick, N. J., 1954.

This monograph is a report of the proceedings of the Tenth Annual Conference on Protein Metabolism, sponsored by the Bureau of Biological Research, at Rutgers University. It is highly technical, concerning primarily the fundamental study of the nature of the precipitin reaction and how this reaction reveals the basic structure of proteins, as well as how the steps in their synthesis and degradation occur.

The first of the six topics considered, proteins as antigens and antibodies, is discussed by Felix Haurowitz. The use of trace-labeled proteins in demonstrating a two-phase process in the formation of antibody protein is reported.

This is followed by a report on the precipitin reaction and studies of native and denatured proteins and derivatives, by Michael Heidelberger. The precise knowledge that accrued with the advent of quantitative antibody estimation is reviewed.

The third report, by David Gitlin, deals with light scattering and ultracentrifugation methods in studies of precipitin systems and their application to human metabolism. The mechanisms of protein deficiency in afibrinogenemia and agammaglobulinemia and studies of the dynamic equilibrium between the intravascular and extravascular protein pools are discussed.

Next, Melvin Cohn discusses the immunological analysis of the biosynthesis of a protein. His report of protein synthesis as a virtually irreversible reaction is perhaps the most significant recent development in the field.

The last report, by Alan Boyden, covers the measurement and significance of serological correspondence among proteins, with especial evaluation of the methods of comparative serology.

The Year Book of Endocrinology. Edited by Gilbert S. Gordon, M.D., Ph.D. Price, $6.00. Pp. 390, with 99 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1954.

As in past years, this book is an excellent review of the current literature in the field of endocrinology. In the present volume, which covers most of the significant articles in endocrinology which appeared in 1953, the abstracts are written in a clear, concise, readable style. The editor has done well to present the main facts of the articles in relatively few words. Abstracts of the papers dealing with the same aspects of endocrinology are grouped under 10 main headings: the pituitary gland, the thyroid gland, the parathyroid glands and calcium metabolism, the adrenal medulla, the adrenal cortex, intersexuality, female reproductive system, the testes, carbohydrate metabolism and diabetes mellitus, and endocrine treatment of neoplastic diseases. Interspersed liberally through the volume are comments by the editor which add much to the interest and value of the book. The comments include many dogmatic statements; moreover, some theories regarding endocrinologic physiology which are held by the editor but which are not accepted by many other endocrinologists are stated as facts. This does not detract seriously from the book, however, and it is well worth reading by any physician interested in endocrinology.

Human Factors in Air Transportation. By Ross A. McFarland. Price, $13.00. Pp. 830. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 18, 1953.

This book is a comprehensive compendium of present-day knowledge of medical and related factors in the transportation of persons by air. It is divided into eight sections, encompassing the selection and maintenance of health of air crews and ground personnel, the health and care of passengers aloft, and sanitation in airline operations.

The part on the selection and training of flight personnel emphasizes the need for integration of the physical standards with the requirements of the job. The author also brings out the importance of criteria other than physical standards in the selection of airmen, such as psychiatric evaluation, psychologic appraisal, job analysis, and determination of pilot performance by flight checks.

The chronic and ever-present aviation medical problem of operational fatigue is reviewed, but, in view of the tremendous number of operational and personal variables in this complex problem, the findings and recommendations of necessity are somewhat inconclusive.

A large part of the book is concerned with the industrial medical aspect of aviation. In the discussion of these problems there is much that would be applicable to other fields of industry. There is also a detailed description of the many problems associated with ascents to extremely high altitudes and high speed of planes, problems which are not of specific interest to the physician. The author's description of them does serve as a preview of aviation medical problems of the future.

Because of the large number of ill people now being transported by plane, the physician will be especially interested in the chapter on the transportation of patients by air. The contraindications to air travel are discussed, and precautionary and therapeutic measures to be taken in such cases are outlined.

It may be that the author is overly conservative in discussing the medical contraindications to flight, but such an attitude probably is best in view of our somewhat incomplete knowledge concerning all the factors affecting the patient in flight.

There are excellent tables summarizing the airline and military experience in the transportation of patients by plane and the contraindications to such travel; these tables constitute a ready reference for the physician confronted with this problem. The cardiovascular and pulmonary contraindications to flight are given much attention and furnish an excellent background of information which will be of aid in arrival at a decision regarding the advisability of an individual's flying.

The material is well presented, and the organization of the book is excellent for reference purposes. The book is of primary interest to the physician or layman interested in airline problems.

Gourmet Cooking for Cardiac Diets. By Florence Field. Price, $3.50. Pp. 350. World Publishing Company, 2231 West 110th St., Cleveland 2, 1953.

How to make food interesting to the heart patient on a salt-free diet has long been a problem to cook and patient alike.

This cookbook supplies an answer to the problems of the salt-free diet and contains numerous well-planned meals falling within the arbitrary scope of the diet already prescribed. The recipes have been kitchen tested, are simple to prepare, and with slight additions may be served to and enjoyed by the whole family. The meals are planned to give variety to the menus and to please the individual taste.

Included are the following: diet lists; menu patterns and recipes; the reducing diet; the low-sodium diet, the low-fat, low-cholesterol diet, and the purine diet, plus many charts, tables, lists of manufacturers of special foods, and other useful information not readily available. The chapter on reducing diets is valuable not only to the cardiac patient but to anyone who wishes to lose weight. It emphasizes the only sane and safe way to reduce and contains not only many lists but also recipes which show how low-caloric food may be prepared, using special dietetic foods and sugar substitutes. This book is a valuable guide to helping the patient with heart disease enjoy his meals without departing from his diet.

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1. Kroop, I. G. and Shackman, N. H.: Proc. Soc. Exper. Biol. & Med. 86:95 (May) 1954.
2. Wood, H. F., and McCarty, M.: J. Clin. Investigation 30:616 (June) 1951.
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4. Hedlund, P.: Acta med. Scandinav., Supplement 196:579, 1947.

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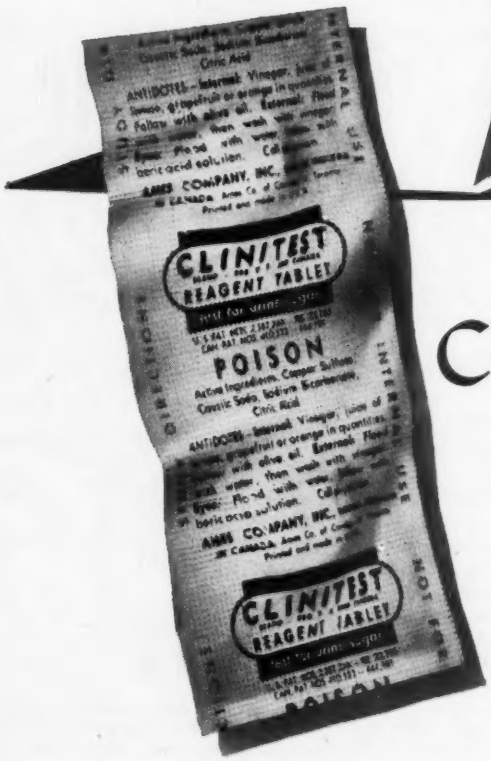

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1. Rev. Gastroenterology 20:744 (Oct.) 1953; abstract in J. A. M. A., 153:1580 (Dec. 26) 1953.

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Bargen, J. A.: Med. Clin. North America, 33:935 (July) 1949.

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Personal communication (Apr. 12)

1951 After-control data 1949 from 119 patients treated with Azulfidine prior to 1944 showed 90 patients (84%) symptom-free or considerably improved.

Svartz, N.: Acta Med. Scandinav. 141:172, 1951.

1952 In a series of 52 patients with chronic ulcerative colitis 30 or 58% showed significant improvement after treatment with Azulfidine.

Morrison, L. M.: Gastroenterology 21:133, 1952.

1953 Morrison publishes results from a series of 47 patients treated with Azulfidine compared to a control series of 60 patients receiving other current therapy: In the Azulfidine-series 18% are symptom-free and 52% improved, compared to 5% and 32% respectively, in the control series.

J. A. M. A.: 151:366 (Jan. 31) 1953.

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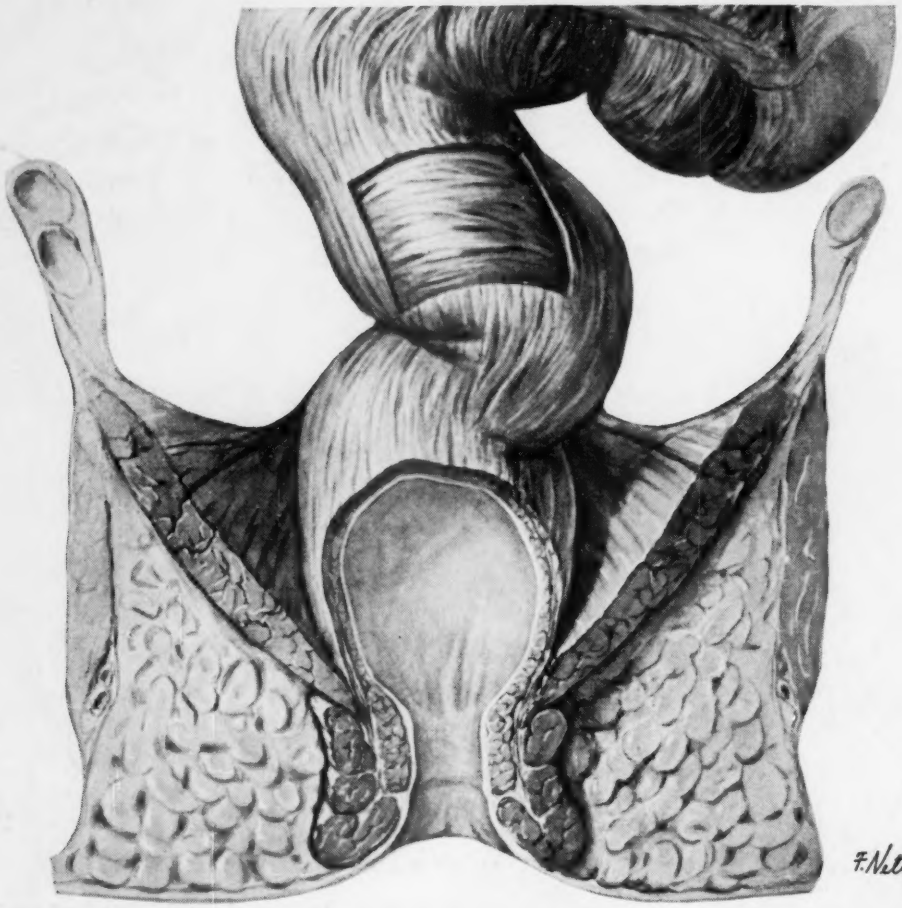

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